

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
24 April 2003 (24.04.2003)

PCT

(10) International Publication Number
WO 03/033453 A1

(51) International Patent Classification⁷: C07C 69/734,
59/68, 229/36, 59/90, A61K 31/225, 31/194, A61P 9/00,
3/06, 3/10, 3/04, C07C 69/712, 323/21

(21) International Application Number: PCT/DK02/00692

(22) International Filing Date: 15 October 2002 (15.10.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PA 2001 01524 17 October 2001 (17.10.2001) DK

(71) Applicant: NOVO NORDISK A/S [DK/DK]; Novo Allé,
DK-2880 Bagsværd (DK).

(81) Designated States (*national*): AE, AG, AI, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC,
VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK,
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(72) Inventors: SAUERBERG, Per; Syrenvænget 27,
DK-3520 Farum (DK). BURY, Paul, Stanley; 75 Athol
Street South, Burnley, Lancashire BB11 4PA (GB).
JEPPESEN, Lone; Malmlosevej 121, DK-2830 Virum
(DK). MOGENSEN, John, Patrick; Rørløkken 96,
DK-2730 Herlev (DK).

(54) Title: DICARBOXYLIC ACID DERIVATIVES, THEIR PREPARATION AND THERAPEUTICAL USE

(57) Abstract: A novel class of dicarboxylic acid derivatives, the use of these compounds as pharmaceutical compositions, pharmaceutical compositions comprising the compounds and methods of treatment employing these compounds and compositions. The present compounds may be useful in the treatment and/or prevention of conditions mediated by Peroxisome Proliferator-Activated Receptors (PPAR).



WO 03/033453 A1

DICARBOXYLIC ACID DERIVATIVES, THEIR PREPARATION AND THERAPEUTICAL USE

FIELD OF THE INVENTION

The present invention relates to novel dicarboxylic acid derivatives, to the use of these compounds as pharmaceutical compositions, to pharmaceutical compositions comprising the compounds and to a method of treatment employing these compounds and compositions. More specifically, the compounds of the invention can be utilised in the treatment and/or prevention of conditions mediated by the Peroxisome Proliferator-Activated Receptors (PPAR).

BACKGROUND OF THE INVENTION

Coronary artery disease (CAD) is the major cause of death in Type 2 diabetic and metabolic syndrome patients (i.e. patients that fall within the 'deadly quartet' category of impaired glucose tolerance, insulin resistance, hypertriglyceridaemia and/or obesity).

The hypolipidaemic fibrates and antidiabetic thiazolidinediones separately display moderately effective triglyceride-lowering activities although they are neither potent nor efficacious enough to be a single therapy of choice for the dyslipidaemia often observed in Type 2 diabetic or metabolic syndrome patients. The thiazolidinediones also potently lower circulating glucose levels of Type 2 diabetic animal models and humans. However, the fibrate class of compounds are without beneficial effects on glycaemia. Studies on the molecular actions of these compounds indicate that thiazolidinediones and fibrates exert their action by activating distinct transcription factors of the peroxisome proliferator activated receptor (PPAR) family, resulting in increased and decreased expression of specific enzymes and apolipoproteins respectively, both key-players in regulation of plasma triglyceride content. Fibrates, on the one hand, are PPAR α activators, acting primarily in the liver. Thiazolidinediones, on the other hand, are high affinity ligands for PPAR γ acting primarily on adipose tissue.

Adipose tissue plays a central role in lipid homeostasis and the maintenance of energy balance in vertebrates. Adipocytes store energy in the form of triglycerides during periods of nutritional affluence and release it in the form of free fatty acids at times of nutritional deprivation. The development of white adipose tissue is the result of a continuous differentiation process throughout life. Much evidence points to the central role of PPAR γ activation in initiating and regulating this cell differentiation. Several highly specialised proteins are induced during adipocyte differentiation, most of them being involved in lipid storage and metabolism. The exact link from activation of PPAR γ to changes in glucose

metabolism, most notably a decrease in insulin resistance in muscle, has not yet been clarified. A possible link is via free fatty acids such that activation of PPAR γ induces Lipoprotein Lipase (LPL), Fatty Acid Transport Protein (FATP) and Acyl-CoA Synthetase (ACS) in adipose tissue but not in muscle tissue. This, in turn, reduces the concentration of free fatty acids in plasma dramatically, and due to substrate competition at the cellular level, skeletal muscle and other tissues with high metabolic rates eventually switch from fatty acid oxidation to glucose oxidation with decreased insulin resistance as a consequence.

PPAR α is involved in stimulating β -oxidation of fatty acids. In rodents, a PPAR α -mediated change in the expression of genes involved in fatty acid metabolism lies at the basis of the phenomenon of peroxisome proliferation, a pleiotropic cellular response, mainly limited to liver and kidney and which can lead to hepatocarcinogenesis in rodents. The phenomenon of peroxisome proliferation is not seen in man. In addition to its role in peroxisome proliferation in rodents, PPAR α is also involved in the control of HDL cholesterol levels in rodents and humans. This effect is, at least partially, based on a PPAR α -mediated transcriptional regulation of the major HDL apolipoproteins, apo A-I and apo A-II. The hypotriglyceridemic action of fibrates and fatty acids also involves PPAR α and can be summarised as follows: (I) an increased lipolysis and clearance of remnant particles, due to changes in lipoprotein lipase and apo C-III levels, (II) a stimulation of cellular fatty acid uptake and their subsequent conversion to acyl-CoA derivatives by the induction of fatty acid binding protein and acyl-CoA synthase, (III) an induction of fatty acid β -oxidation pathways, (IV) a reduction in fatty acid and triglyceride synthesis, and finally (V) a decrease in VLDL production. Hence, both enhanced catabolism of triglyceride-rich particles as well as reduced secretion of VLDL particles constitutes mechanisms that contribute to the hypolipidemic effect of fibrates.

PPAR δ activation was initially reported not to be involved in modulation of glucose or triglyceride levels. (Berger et al., *J. Biol. Chem.*, 1999, Vol 274, pp. 6718-6725). Later it has been shown that PPAR δ activation leads to increased levels of HDL cholesterol in db/db mice (Leibowitz et al. FEBS letters 2000, 473, 333-336). Further, a PPAR δ agonist when dosed to insulin-resistant middle-aged obese rhesus monkeys caused a dramatic dose-dependent rise in serum HDL cholesterol while lowering the levels of small dense LDL, fasting triglycerides and fasting insulin (Oliver et al. PNAS 2001, 98, 5306-5311). The same paper also showed that PPAR δ activation increased the reverse cholesterol transporter ATP-binding cassette A1 and induced apolipoprotein A1-specific cholesterol efflux. Taken together these observations suggest that PPAR δ activation is useful in the treatment and

prevention of cardiovascular diseases and conditions including atherosclerosis, hypertriglyceridemia, and mixed dyslipidaemia (PCT publication WO 01/00603 (Chao et al.).

A number of compounds have been reported to be useful in the treatment of hyperglycemia, hyperlipidemia and hypercholesterolemia (U.S. Pat. 5,306,726, PCT Publications
5 nos. WO91/19702, WO 95/03038, WO 96/04260, WO 94/13650, WO 94/01420, WO 97/36579, WO 97/25042, WO 95/17394, WO 99/08501, WO 99/19313, WO 99/16758 and WO 01/00603). WO 99/63983 discloses multibinding compounds, which bind to PPAR γ receptors.

Glucose lowering as a single approach does not overcome the macrovascular complications associated with Type 2 diabetes and metabolic syndrome. Novel treatments of
10 Type 2 diabetes and metabolic syndrome must therefore aim at lowering both the overt hypertriglyceridaemia associated with these syndromes as well as alleviation of hyperglycaemia.

This indicate that research for compounds displaying various degree of PPAR α ,
15 PPAR γ and PPAR δ activation should lead to the discovery of efficacious triglyceride and/or cholesterol and/or glucose lowering drugs that have great potential in the treatment of diseases such as type 2 diabetes, dyslipidemia, syndrome X (including the metabolic syndrome, i.e. impaired glucose tolerance, insulin resistance, hypertriglyceridaemia and/or obesity), cardiovascular diseases (including atherosclerosis) and hypercholesterolemia.

20 DEFINITIONS

In the structural formulas given herein and throughout the present specification the following terms have the indicated meaning:

The terms "C_{1-n}-alkyl" wherein n' can be from 2 through 6, as used herein, represent a linear or branched, saturated hydrocarbon chain having the indicated number of carbon
25 atoms. Examples of such groups include, but are not limited to methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec-butyl, *tert*-butyl, pentyl, isopentyl, hexyl, isohexyl and the like.

The term "C_{3-n}-cycloalkyl" wherein n' can be from 4 through 6, as used herein, alone or in combination, represent a saturated monocyclic hydrocarbon group having the indicated number of carbon atoms. Examples of such groups include, but are not limited to cyclopropyl,
30 cyclobutyl, cyclopentyl, cyclohexyl and the like.

The terms "C_{1-n}-alkylene" wherein n' can be from 2 through 6, as used herein, represent a divalent linear or branched, saturated hydrocarbon chain having the indicated number of carbon atoms. Examples of such groups include, but are not limited to methylene,

ethylene, trimethylene, tetramethylene, propylene, ethylethylene, methylpropylene, ethylpropylene and the like.

The terms " C_{4-n} -cycloalkylene" wherein n' can be from 5 through 6, as used herein, represent a divalent saturated monocyclic hydrocarbon group having the indicated number of carbon atoms. Examples of such groups include, but are not limited to cyclopentylene, cyclohexylene and the like.

The term " C_{2-n} -alkenyl" wherein n' can be from 3 through 6, as used herein, represent an olefinically unsaturated branched or straight hydrocarbon group having from 2 to the specified number of carbon atoms and at least one double bond. Examples of such groups include, but are not limited to, vinyl, 1-propenyl, 2-propenyl, allyl, iso-propenyl, 1,3-butadienyl, 1-butenyl, hexenyl, pentenyl and the like.

The term " C_{2-n} -alkenylene" wherein n' can be from 3 through 6, as used herein, represent an divalent olefinically unsaturated branched or straight hydrocarbon group having from 2 to the specified number of carbon atoms and at least one double bond. Examples of such groups include, but are not limited to ethenylene ($-CH=CH-$), the propenylene isomers (e.g., $-CH_2CH=CH-$ and $-C(CH_3)=CH-$), the butenylene isomers (e.g., $-CH_2CH=C(CH_3)-$ and $-CH_2CH_2CH=CH-$) and the like.

The terms " C_{4-n} -alkenynyl" as used herein, represent an unsaturated branched or straight hydrocarbon group having from 4 to the specified number of carbon atoms and both at least one double bond and at least one triple bond. Examples of such groups include, but are not limited to, 1-penten-4-yne, 3-penten-1-yne, 1,3-hexadiene-5-yne and the like, especially preferred is 1-pentene-4-yne.

The term " C_{4-n} -cycloalkenylene" wherein n' can be from 5 through 6, as used herein, represent an divalent unsaturated monocyclic hydrocarbon group having from 4 to the specified number of carbon atoms and at least one double bond. Examples of such groups include, but are not limited to cyclohexenylene and the like.

The term " C_{3-n} -alkynyl" wherein n' can be from 4 through 6, as used herein, represent an unsaturated branched or straight hydrocarbon group having from 2 to the specified number of carbon atoms and at least one triple bond. Examples of such groups include, but are not limited to, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 1-pentylnyl, 2-pentylnyl and the like.

The term " C_{2-n} -alkynylene" wherein n' can be from 3 through 6, as used herein, represent an divalent unsaturated branched or straight hydrocarbon group having from 2 to the specified number of carbon atoms and at least one triple bond. Examples of such groups

include, but are not limited to, propynylene ($-\text{CH}_2\text{C}\equiv\text{C}-$), the butynylene isomers (e.g., $-\text{CH}_2\text{CH}_2\text{C}\equiv\text{C}-$, $-\text{CH}_2\text{C}\equiv\text{C}-\text{CH}_2-$), and the like.

The term " C_{4-n} -alkenynylene" wherein n' can be from 5 through 9 as used herein, represent an divalent unsaturated branched or straight hydrocarbon group having from 4 to
5 the specified number of carbon atoms and both at least one double bond and at least one triple bond. Examples of such groups include, but are not limited to, 1-penten-4-ynylene, 3-penten-1-ynylene, 1,3-hexadiene-5-ynylene and the like.

The term " C_{3-n} -divalent unsaturated carbon chain" wherein n' can be from 4 through 9, as used herein, represent an divalent unsaturated branched or straight hydrocarbon group
10 having from 3 to the specified number of carbon atoms and at least one double bond (alkenylene) or at least one triple bond (alkynylene) or a combination hereof (alkenynylene). Examples of such groups include, but are not limited to ethenylene ($-\text{CH}=\text{CH}-$), the propenylene isomers (e.g., $-\text{CH}_2\text{CH}=\text{CH}-$ and $-\text{C}(\text{CH}_3)=\text{CH}-$), the butenylene isomers (e.g., $-\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)-$ and $-\text{CH}_2\text{CH}_2\text{CH}=\text{CH}-$), propynylene ($-\text{CH}_2\text{C}\equiv\text{C}-$), the butynylene isomers
15 (e.g., $-\text{CH}_2\text{CH}_2\text{C}\equiv\text{C}-$, $-\text{CH}_2\text{C}\equiv\text{C}-\text{CH}_2-$), 1-penten-4-ynylene, 3-penten-1-ynylene, 1,3-hexadiene-5-ynylene and the like.

The term " C_{1-n} -alkoxy" wherein n' can be from 2 through 6, as used herein, alone or in combination, refers to a straight or branched configuration linked through an ether oxygen having its free valence bond from the ether oxygen. Examples of such linear alkoxy groups
20 include, but are not limited to methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy and the like. Examples of such branched alkoxy include, but are not limited to isopropoxy, sec-butoxy, tert-butoxy, isopentyloxy, isohexyloxy and the like.

The term " C_{3-n} -cycloalkoxy" wherein n' can be from 4 through 6, as used herein, alone or in combination, represent a saturated monocyclic hydrocarbon group having the
25 indicated number of carbon atoms linked through an ether oxygen having its free valence bond from the ether oxygen. Examples of such cycloalkoxy groups include, but are not limited to cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and the like.

The term " C_{1-n} -alkylthio" wherein n' can be from 2 through 6, as used herein, alone or in combination, refers to a straight or branched monovalent substituent comprising a C_{1-6} -
30 alkyl group linked through a divalent sulfur atom having its free valence bond from the sulfur atom and having 1 to 6 carbon atoms. Examples of such groups include, but are not limited to methylthio, ethylthio, propylthio, butylthio, pentylthio and the like.

The term " C_{3-n} -cycloalkylthio" wherein n' can be from 4 through 6, as used herein, alone or in combination, represent a saturated monocyclic hydrocarbon group having the
35 indicated number of carbon atoms linked through a divalent sulfur atom having its free valence

bond from the sulfur atom. Examples of such cycloalkoxy groups include, but are not limited to cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio and the like.

The term "aryl" as used herein refers to an aromatic monocyclic or an aromatic fused bi- or tricyclic hydrocarbon group. Examples of such groups include, but are not limited to phenyl, naphthyl, anthracenyl, phenanthrenyl, azulenyl and the like.

The term "arylene" as used herein refers to divalent aromatic monocyclic or a divalent aromatic fused bi- or tricyclic hydrocarbon group (derived from aryl). Examples of such groups include, but are not limited to phenylene, naphthylene and the like.

The term "heteroaryl" as used herein, alone or in combination, refers to a divalent substituent comprising a 5-7 membered monocyclic aromatic system or a 8-10 membered bicyclic fused aromatic system containing one or more heteroatoms selected from nitrogen, oxygen and sulfur or a 10-16 membered tricyclic fused aromatic system containing one or more heteroatoms selected from nitrogen, oxygen and sulfur e.g. furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, isothiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, indolyl, benzimidazolyl, benzofuranyl, pteridinyl, purinyl, carbazolyl, β -carbolinyl, acridinyl, phenanthrolinyl, phenazinyl, phenoxazinyl, phenothiazinyl and the like

The term "heteroarylene" as used herein, alone or in combination, refers to a divalent substituent (derived from heteroaryl) comprising a 5-7 membered monocyclic aromatic system or a 8-10 membered bicyclic aromatic system containing one or more heteroatoms selected from nitrogen, oxygen and sulfur or a 10-16 membered tricyclic fused aromatic system containing one or more heteroatoms selected from nitrogen, oxygen and sulfur e.g. furylene, thienylene, pyrrolylene, imidazolylene, pyrazolylene, triazolylene, pyrazinylene, pyrimidinylene, pyridazinylene, isothiazolylene, isoxazolylene, oxazolylene, oxadiazolylene, thiadiazolylene, quinolylene, isoquinolylene, quinazolinylene, quinoxalinylene, indolylene, benzimidazolylene, benzofuranylene, pteridinylene, purinylene, carbazolylene, β -carbolinylene, acridinylene, phenanthrolinylene, phenazinylene, phenoxazinylene, phenothiazinylene and the like.

The term "a divalent polycyclic ringsystem" as used herein refers to a divalent group formed from a polycyclic ringsystem containing indenpending of each other 2 trough 4 aryl or heteroaryl ring systems joined by single bonds. Example of such bi-, ter- and quaterarylene having 2 through 4 identical aryl ring systems include, but are not limited to biphenylene, binaphthylene, terphenylene, ternaphthylene, quaterphenylene, quaternaphthylene and the like. Example of such bi-, ter- and quaterheteroarylene having 2 through 4 identical heteroaryl ring systems include, but are not limited to bipyridylene, biindolylene, terpyridyl-

ylene, terindolylylene, quaterpyridylylene, quaterindolylylene and the like. Example of such polycyclic ringsystems having non identical ring systems include, but are not limited to diphenylpyridine and the like.

The term "aralkoxy" as used herein refers to a C₁₋₆-alkoxy group substituted with an aromatic carbohydride, such as benzyloxy, phenethoxy, 3-phenylpropoxy, 1-naphthylmethoxy, 2-(1-naphthyl)ethoxy and the like.

The term "aralkyl" as used herein refers to a straight or branched saturated carbon chain containing from 1 to 6 carbons substituted with an aromatic carbohydride; such as benzyl, phenethyl, 3-phenylpropyl, 1-naphthylmethyl, 2-(1-naphthyl)ethyl and the like.

The term "halogen" means fluorine, chlorine, bromine or iodine.

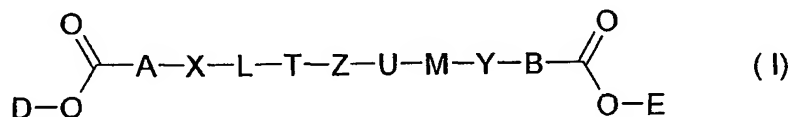
The term "treatment" as used herein includes treatment, prevention and management of conditions mediated by Peroxisome Proliferator-Activated Receptors (PPAR).

Certain of the above defined terms may occur more than once in the structural formulae, and upon such occurrence each term shall be defined independently of the other.

The term "optionally substituted" as used herein means that the groups in question are either unsubstituted or substituted with one or more of the substituents specified. When the groups in question are substituted with more than one substituent the substituents may be the same or different.

DESCRIPTION OF THE INVENTION

The present invention relates to compounds of the general formula (I):



wherein A is C₁₋₃-alkylene which is optionally substituted with one or more substituents selected from

- halogen or
- C₁₋₃-alkyl, C₁₋₆-alkoxy, C₃₋₆-cycloalkoxy, C₁₋₆-alkylthio, C₃₋₆-cycloalkylthio or aralkoxy each of which is optionally substituted with halogen; or
- NR₁R₂ wherein R₁ represents hydrogen or C₁₋₃-alkyl and R₂ represents -R₃- (C=O)-R₄ wherein:

- o R₃ represents C₁₋₆-alkylene, C₂₋₆-alkenylene, C₄₋₆-cycloalkylene, C₄₋₆-cycloalkenylene, or arylene optionally substituted with one or more halogens;
- o R₄ represents aryl optionally substituted with one or more halogens; or

5

A is -O-A' or -S-A' wherein -O- or -S- is linked to X in formula (I) and wherein A' is C₁₋₃-alkylene which is optionally substituted with one or more substituents selected from

- halogen or
- C₁₋₃-alkyl, C₁₋₆-alkoxy, C₃₋₆-cycloalkoxy, C₁₋₆-alkylthio, C₃₋₆-cycloalkylthio or aralkoxy each of which is optionally substituted with halogen; or
- NR₁R₂ wherein R₁ represents hydrogen or C₁₋₃-alkyl and R₂ represents -R₃-(C=O)-R₄ wherein:
 - o R₃ represents C₁₋₆-alkylene, C₂₋₆-alkenylene, C₄₋₆-cycloalkylene, C₄₋₆-cycloalkenylene, or arylene optionally substituted with one or more halogens;
 - o R₄ represents aryl optionally substituted with one or more halogens; and

15

B is C₁₋₃-alkylene which is optionally substituted with one or more substituents selected from

- halogen or
- C₁₋₃-alkyl, C₁₋₆-alkoxy, C₃₋₆-cycloalkoxy, C₁₋₆-alkylthio, C₃₋₆-cycloalkylthio or aralkoxy each of which is optionally substituted with halogen; or
- NR₁R₂ wherein R₁ represents hydrogen or C₁₋₃-alkyl and R₂ represents -R₃-(C=O)-R₄ wherein:
 - o R₃ represents C₁₋₆-alkylene, C₂₋₆-alkenylene, C₄₋₆-cycloalkylene, C₄₋₆-cycloalkenylene, or arylene optionally substituted with one or more halogens;
 - o R₄ represents aryl optionally substituted with one or more halogens; or

20

25

B is -O-B' or -S-B' wherein -O- or -S- is linked to Y in formula (I) and wherein B' is C₁₋₃-alkylene which is optionally substituted with one or more substituents selected from

- halogen or
- C₁₋₃-alkyl, C₁₋₆-alkoxy, C₃₋₆-cycloalkoxy, C₁₋₆-alkylthio, C₃₋₆-cycloalkylthio or aralkoxy each of which is optionally substituted with halogen; or
- NR₁R₂ wherein R₁ represents hydrogen or C₁₋₃-alkyl and R₂ represents -R₃-(C=O)-R₄ wherein:

35

- R₃ represents C₁₋₆-alkylene, C₂₋₆-alkenylene, C₄₋₆-cycloalkylene, C₄₋₆-cycloalkenylene, or arylene optionally substituted with one or more halogens;
- R₄ represents aryl optionally substituted with one or more halogens; and

5

D is H, C₁₋₆-alkyl or C₃₋₆-cycloalkyl; and

E is H, C₁₋₆-alkyl or C₃₋₆-cycloalkyl; and

10

L and M are independently -O- or -S-; and

T is C₃₋₉ divalent unsaturated carbon chain optionally substituted with one or more substituents selected from

- 15
- halogen or hydroxy; or
 - aryl, aralkoxy or C₁₋₃-alkoxy which is optionally substituted with halogen; and

U is C₃₋₉ divalent unsaturated carbon chain optionally substituted with one or more substituents selected from

- 20
- halogen or hydroxy; or
 - aryl, aralkoxy or C₁₋₃-alkoxy which is optionally substituted with halogen; and

X is arylene or heteroarylene each of which is optionally substituted with one or more substituents selected from

- 25
- halogen or hydroxy; or
 - C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₁₋₆-alkoxy, C₃₋₆-cycloalkoxy, C₁₋₆-alkylthio, C₃₋₆-cycloalkylthio each of which is optionally substituted with one or more halogen; or

Y is arylene or heteroarylene each of which is optionally substituted with one or more substituents selected from

- 30
- halogen or hydroxy; or
 - C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₁₋₆-alkoxy, C₃₋₆-cycloalkoxy, C₁₋₆-alkylthio, C₃₋₆-cycloalkylthio each of which is optionally substituted with one or more halogen; or

35

Z is arylene, heteroarylene or a divalent polycyclic ringsystem each of which is optionally substituted with one or more substituents selected from

- halogen, oxo or hydroxy; or
- C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₁₋₆-alkoxy, C₃₋₆-cycloalkoxy, C₁₋₆-alkylthio, C₃₋₆-cycloalkylthio each of which is optionally substituted with one or more halogen; or

5 a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, or any tautomeric forms, stereoisomers, mixture of stereoisomers including a racemic mixture, or polymorphs.

10 In one embodiment, the present invention is concerned with compounds of formula (I) wherein A is C₁₋₃-alkylene which is optionally substituted with one or more substituents selected from

- methyl, C₁₋₃-alkoxy, C₃₋₆-cycloalkoxy or benzyloxy each of which is optionally substituted with halogen; or
- NR₁R₂ wherein R₁ represents hydrogen and R₂ represents -R₃-(C=O)-R₄ wherein:
 - 15 o R₃ represents C₁₋₆-alkylene, C₂₋₆-alkenylene, C₄₋₆-cycloalkylene, C₄₋₆-cycloalkenylene, or phenylene optionally substituted with one or more halogens;
 - o R₄ represents phenyl optionally substituted with one or more halogens.

20 In another embodiment, the present invention is concerned with compounds of formula (I) wherein A is methylene or ethylene each of which is optionally substituted with one or more substituents selected from

- methoxy or ethoxy; or
- NR₁R₂ wherein R₁ represents hydrogen and R₂ represents -R₃-(C=O)-R₄ wherein
 - 25 R₃ and R₄ represents phenyl.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein A is ethylene which is optionally substituted with ethoxy.

30 In another embodiment, the present invention is concerned with compounds of formula (I) wherein A is -O-A' or -S-A' wherein -O- or -S- is linked to X in formula (I) and wherein A' is C₁₋₃-alkylene which is optionally substituted with one or more substituents selected from

- halogen or
- C₁₋₃-alkyl, C₁₋₆-alkoxy, C₃₋₆-cycloalkoxy or aralkoxy each of which is optionally
 - 35 substituted with halogen.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein A is -O-A' or -S-A' wherein -O- or -S- is linked to X in formula (I) and wherein A' is methylene or ethylene each of which is optionally substituted with one or more substituents selected from methyl, methoxy or ethoxy.

- In another embodiment, the present invention is concerned with compounds of formula (I) wherein B is C₁₋₃-alkylene, which is optionally substituted with one or more substituents selected from
- methyl, C₁₋₃-alkoxy, C₃₋₆-cycloalkoxy or benzyloxy each of which is optionally substituted with halogen; or
 - NR₁R₂ wherein R₁ represents hydrogen and R₂ represents -R₃-(C=O)-R₄ wherein:
 - R₃ represents C₁₋₆-alkylene, C₂₋₆-alkenylene, C₄₋₆-cycloalkylene, C₄₋₆-cycloalkenylene, or phenylene optionally substituted with one or more halogens;
 - R₄ represents phenyl optionally substituted with one or more halogens.

- In another embodiment, the present invention is concerned with compounds of formula (I) wherein B is methylene or ethylene each of which is optionally substituted with one or more substituents selected from
- methoxy or ethoxy; or
 - NR₁R₂ wherein R₁ represents hydrogen and R₂ represents -R₃-(C=O)-R₄ wherein R₃ and R₄ represents phenyl.

- In another embodiment, the present invention is concerned with compounds of formula (I) wherein B is ethylene which is optionally substituted with ethoxy.

- In another embodiment, the present invention is concerned with compounds of formula (I) wherein B is -O-B' or -S-B' wherein -O- or -S- is linked to Y in formula (I) and wherein B' is C₁₋₃-alkylene which is optionally substituted with one or more substituents selected from
- halogen or
 - C₁₋₃-alkyl, C₁₋₆-alkoxy, C₃₋₆-cycloalkoxy or aralkoxy each of which is optionally substituted with halogen.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein B is -O-B' or -S-B' wherein -O- or -S- is linked to Y in formula (I) and wherein B' is methylene or ethylene each of which is optionally substituted with one or more substituents selected from methyl, methoxy or ethoxy.

5

In another embodiment, the present invention is concerned with compounds of formula (I) wherein D is H.

10 In another embodiment, the present invention is concerned with compounds of formula (I) wherein D is methyl or ethyl.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein E is H.

15

In another embodiment, the present invention is concerned with compounds of formula (I) wherein E is methyl or ethyl.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein L is -O-.

20

In another embodiment, the present invention is concerned with compounds of formula (I) wherein L is -S-.

25 In another embodiment, the present invention is concerned with compounds of formula (I) wherein M is -O-.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein M is -S-.

30

In another embodiment, the present invention is concerned with compounds of formula (I) wherein T is C₃₋₉ divalent unsaturated carbon chain optionally substituted with one or more substituents selected from phenyl, benzyloxy or C₁₋₃-alkoxy which is optionally substituted with halogen.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein T is an unsubstituted C₃₋₉ divalent unsaturated carbon chain.

5 In another embodiment, the present invention is concerned with compounds of formula (I) wherein T is C₃₋₉ alkenylene.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein T is C₃₋₉ alkynylene.

10 In another embodiment, the present invention is concerned with compounds of formula (I) wherein T is C₅₋₉ alkenynylene.

15 In another embodiment, the present invention is concerned with compounds of formula (I) wherein U is C₃₋₉ divalent unsaturated carbon chain optionally substituted with one or more substituents selected from phenyl, benzyloxy or C₁₋₃-alkoxy which is optionally substituted with halogen.

20 In another embodiment, the present invention is concerned with compounds of formula (I) wherein U is an unsubstituted C₃₋₉ divalent unsaturated carbon chain.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein U is C₃₋₉ alkenylene.

25 In another embodiment, the present invention is concerned with compounds of formula (I) wherein U is C₃₋₉ alkynylene.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein U is C₅₋₉ alkenynylene.

30 In another embodiment, the present invention is concerned with compounds of formula (I) wherein X is arylene or heteroarylene each of which is optionally substituted with one or more substituents selected from

- halogen or
- C₁₋₆-alkyl optionally substituted with one or more halogen.

35

In another embodiment, the present invention is concerned with compounds of formula (I) wherein X is arylene optionally substituted with one or more substituents selected from

- halogen or
- C₁₋₆-alkyl optionally substituted with one or more halogen.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein X is phenylene optionally substituted with one or more substituents selected from

- halogen or
- C₁₋₃-alkyl optionally substituted with one or more halogen.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein X is phenylene optionally substituted with one or more halogen.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein Y is arylene or heteroarylene each of which is optionally substituted with one or more substituents selected from

- halogen or
- C₁₋₆-alkyl optionally substituted with one or more halogen.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein Y is arylene optionally substituted with one or more substituents selected from

- halogen or
- C₁₋₆-alkyl optionally substituted with one or more halogen.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein Y is phenylene optionally substituted with one or more substituents selected from

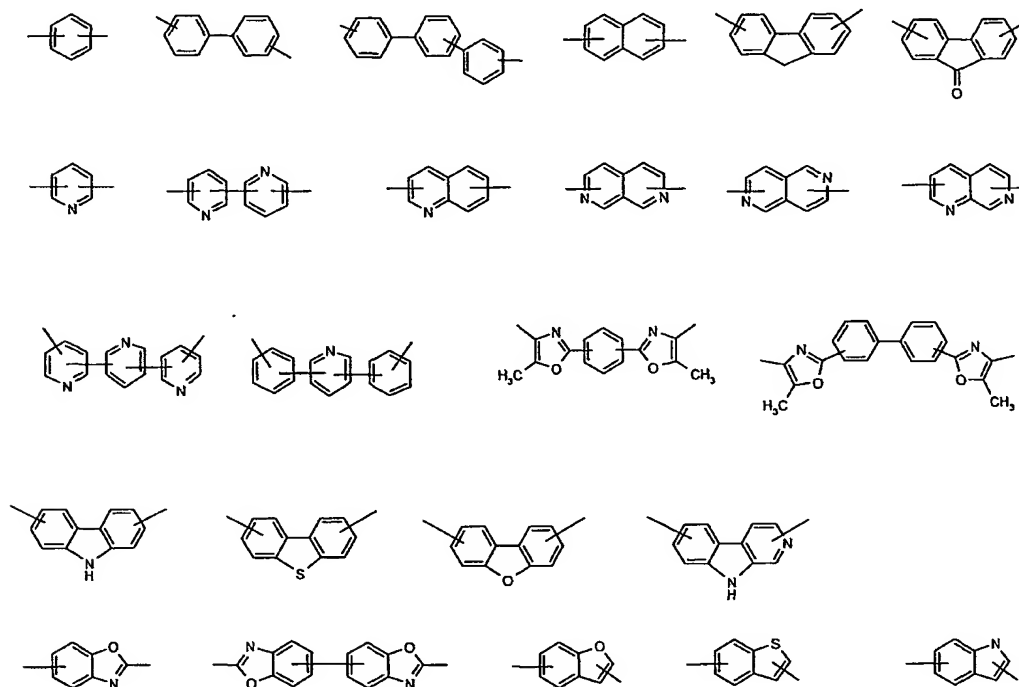
- halogen or
- C₁₋₃-alkyl optionally substituted with one or more halogen.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein Y is phenylene optionally substituted with one or more halogen.

In another embodiment, the present invention is concerned with compounds of formula (I) wherein Z is arylene, heteroarylene or a divalent polycyclic ringsystem each of which is optionally substituted with one or more substituents selected from

- 5
- halogen, oxo or
 - C₁₋₆-alkyl, C₁₋₆-alkoxy each of which is optionally substituted with one or more halogen.

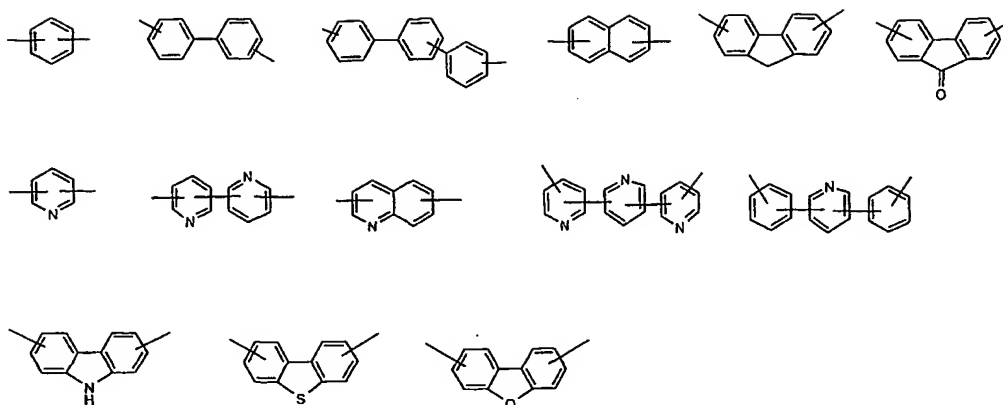
10 In another embodiment, the present invention is concerned with compounds of formula (I) wherein Z is selected among the following groups:



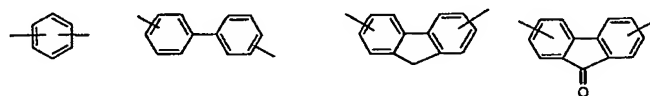
which is optionally substituted with one or more substituents selected from

- 15
- halogen or
 - C₁₋₆-alkyl or C₁₋₆-alkoxy each of which is optionally substituted with one or more halogen.

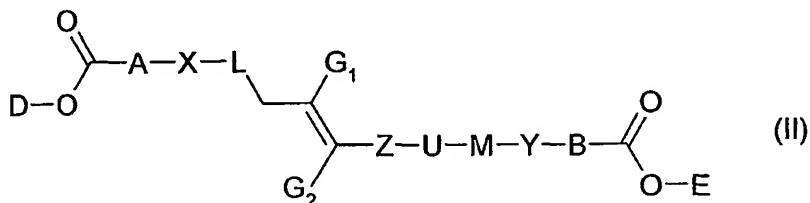
20 In another embodiment, the present invention is concerned with compounds of formula (I) wherein Z is selected among the following groups:



In another embodiment, the present invention is concerned with compounds of formula (I) wherein Z is selected among the following groups:



In another embodiment, the present invention is concerned with compounds of general formula (I) as described by general formula (II)



wherein D, A, X, L, Z, U, M, Y, B and E are as defined for formula (I) or in any of the above preferred embodiments; and

- 15 G₁ is H, C₁₋₃-alkyl, C₁₋₃-alkoxy or C₁₋₃-aralkoxy each of which is optionally substituted with halogen; and
- G₂ is H, C₁₋₃-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₆-alkenynyl, aryl, aralkyl, C₁₋₃-alkoxy or C₁₋₃-aralkoxy each of which is optionally substituted with halogen; or
- a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof,
- 20 or any tautomeric forms, stereoisomers, mixture of stereoisomers including a racemic mixture, or polymorphs.

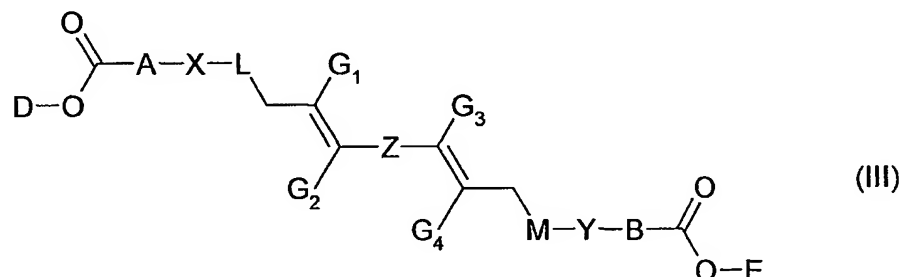
In another embodiment, the present invention is concerned with compounds of formula (II) wherein D, A, X, L, Z, U, M, Y, B and E are as defined for formula (I) or in any of the above preferred embodiments; and

- 5 G_1 is H, C_{1-3} -alkyl or C_{1-3} -alkoxy each of which is optionally substituted with halogen; and
 G_2 is H, C_{1-3} -alkyl or aryl each of which is optionally substituted with halogen.

In another embodiment, the present invention is concerned with compounds of formula (II) wherein D, A, X, L, Z, U, M, Y, B and E are as defined for formula (I) or in any of the above preferred embodiments; and

- G_1 is H; and
 G_2 is H or methyl.

In another embodiment, the present invention is concerned with compounds of general formula (I) as described by general formula (III)



wherein D, A, X, L, Z, M, Y, B and E are as defined for formula (I) or in any of the above preferred embodiments; and

- G_1 and G_4 independently of each other are H, C_{1-3} -alkyl, C_{1-3} -alkoxy or C_{1-3} -aralkoxy each of which is optionally substituted with halogen; and

G_2 and G_3 independently of each other is H, C_{1-3} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-6} -alkenynyl, aryl, aralkyl, C_{1-3} -alkoxy or C_{1-3} -aralkoxy each of which is optionally substituted with halogen; or

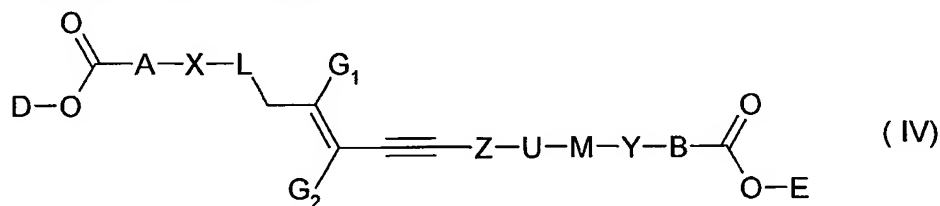
- a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof,
 25 or any tautomeric forms, stereoisomers, mixture of stereoisomers including a racemic mixture, or polymorphs.

In another embodiment, the present invention is concerned with compounds of formula (III) wherein D, A, X, L, Z, M, Y, B and E are as defined for formula (I) or in any of the above preferred embodiments; and

- G₁ and G₄ independently of each other are H, C₁₋₃-alkyl or C₁₋₃-alkoxy each of which is optionally substituted with halogen; and
- G₂ and G₃ independently of each other are H, C₁₋₃-alkyl or aryl each of which is optionally substituted with halogen.

- In another embodiment, the present invention is concerned with compounds of formula (III) wherein D, A, X, L, Z, M, Y, B and E are as defined for formula (I) or in any of the above preferred embodiments; and
- G₁ and G₄ are H; and
- G₂ and G₃ independently of each other are H or methyl.

- In another embodiment, the present invention is concerned with compounds of general formula (I) as described by general formula (IV)



- wherein D, A, X, L, Z, U, M, Y, B and E are as defined for formula (I) or in any of the above preferred embodiments; and
- G₁ is H, C₁₋₃-alkyl, C₁₋₃-alkoxy or C₁₋₃-aralkoxy each of which is optionally substituted with halogen; and
- G₂ is H, C₁₋₃-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₆-alkenynyl, aryl, aralkyl, C₁₋₃-alkoxy or C₁₋₃-aralkoxy each of which is optionally substituted with halogen; or
- a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof,
- or any tautomeric forms, stereoisomers, mixture of stereoisomers including a racemic mixture, or polymorphs.

- In another embodiment, the present invention is concerned with compounds of formula (IV) wherein D, A, X, L, Z, U, M, Y, B and E are as defined for formula (I) or in any of the above preferred embodiments; and
- G₁ is H, C₁₋₃-alkyl or C₁₋₃-alkoxy each of which is optionally substituted with halogen; and

G_2 is H, C_{1-3} -alkyl or aryl each of which is optionally substituted with halogen.

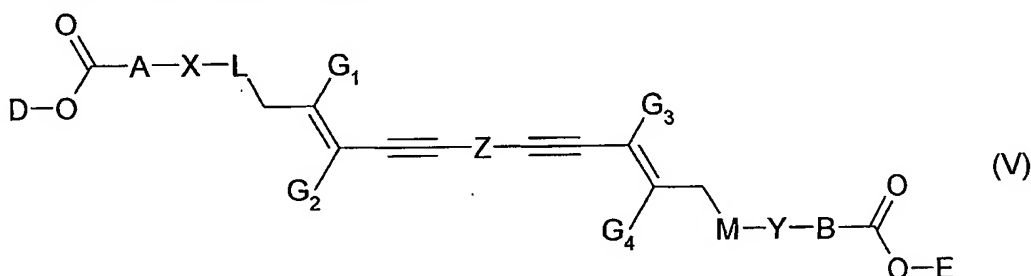
In another embodiment, the present invention is concerned with compounds of formula (IV) wherein D, A, X, L, Z, U, M, Y, B and E are as defined for formula (I) or in any of the

5 above preferred embodiments; and

G_1 is H; and

G_2 is H or methyl.

10 In another embodiment, the present invention is concerned with compounds of general formula (I) as described by general formula (V)



wherein D, A, X, L, Z, M, Y, B and E are as defined for formula (I) or in any of the above preferred embodiments; and

15 G_1 and G_4 independently of each other are H, C_{1-3} -alkyl, C_{1-3} -alkoxy or C_{1-3} -aralkoxy each of which is optionally substituted with halogen; and

G_2 and G_3 independently of each other is H, C_{1-3} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-6} -alkenynyl, aryl, aralkyl, C_{1-3} -alkoxy or C_{1-3} -aralkoxy each of which is optionally substituted with halogen; or

20 a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, or any tautomeric forms, stereoisomers, mixture of stereoisomers including a racemic mixture, or polymorphs.

In another embodiment, the present invention is concerned with compounds of formula (V) wherein D, A, X, L, Z, M, Y, B and E are as defined for formula (I) or in any of the

25 above preferred embodiments; and

G_1 and G_4 independently of each other are H, C_{1-3} -alkyl or C_{1-3} -alkoxy each of which is optionally substituted with halogen; and

G_2 and G_3 independently of each other are H, C_{1-3} -alkyl or aryl each of which is optionally substituted with halogen.

In another embodiment, the present invention is concerned with compounds of formula (V) wherein D, A, X, L, Z, M, Y, B and E are as defined for formula (I) or in any of the above preferred embodiments; and

- 5 G₁ and G₄ are H; and
G₂ and G₃ independently of each other are H or methyl.

In another embodiment, the present invention is concerned with compounds of the present invention having a *trans*-configuration when possible.

- 10 In another embodiment, the present invention is concerned with compounds of the present invention having a (*S*)-configuration when possible.

In another embodiment, the present invention is concerned with compounds of the present invention having a *cis*-configuration when possible.

- 15 In another embodiment, the present invention is concerned with compounds of the present invention which is a mixed PPAR α /PPAR γ profile.

In another embodiment, the present invention is concerned with compounds of the present invention which is a mixed PPAR α /PPAR δ profile.

- In another embodiment, the present invention is concerned with compounds of the present invention which is a mixed PPAR γ /PPAR δ profile.

- 20 In another embodiment, the present invention is concerned with compounds of the present invention which is a mixed PPAR α /PPAR γ /PPAR δ profile.

In another embodiment, the present invention is concerned with compounds of the present invention, which is a selective PPAR α profile.

- 25 In another embodiment, the present invention is concerned with compounds of the present invention, which is a selective PPAR γ profile.

In another embodiment, the present invention is concerned with compounds of the present invention, which is a selective PPAR δ profile.

Examples of specific compounds of the invention are:

- 30 2-Ethoxy-3-{4-[5-(4-{5-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-pent-3-en-1-ynyl}-phenyl)-pent-2-en-4-ynyloxy]-phenyl}-propionic acid ethyl ester;
3-{4-[5-(4-{5-[4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy]-pent-3-en-1-ynyl}-phenyl)-pent-2-en-4-ynyloxy]-phenyl}-2-ethoxy-propionic acid;
3-Chloro-4-(5-{4-[5-(3-Chloro-4-ethoxycarbonylmethyl-phenoxy)-pent-3-en-1-ynyl]-phenyl}-
35 pent-2-en-4-ynyloxy)-phenyl}-acetic acid ethyl ester;

- [4-(5-{4-[5-(4-Carboxymethyl-3-chloro-phenoxy)-pent-3-en-1-ynyl]-phenyl}-pent-2-en-4-ynyloxy)-3-chloro-phenyl]-acetic acid;
- 2-Ethoxy-3-{4-[5-(3-{5-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-pent-3-en-1-ynyl}-phenyl)-pent-2-en-4-ynyloxy]-phenyl}-propionic acid ethyl ester;
- 5 3-{4-[5-(3-{5-[4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy]-pent-3-en-1-ynyl}-phenyl)-pent-2-en-4-ynyloxy]-phenyl}-2-ethoxy-propionic acid;
- [3-Chloro-4-(5-{3-[5-(2-chloro-4-ethoxycarbonylmethyl-phenoxy)-pent-3-en-1-ynyl]-phenyl}-pent-2-en-4-ynyloxy)-phenyl]-acetic acid ethyl ester;
- [4-(5-{3-[5-(4-Carboxymethyl-2-chloro-phenoxy)-pent-3-en-1-ynyl]-phenyl}-pent-2-en-4-ynyloxy)-3-chloro-phenyl]-acetic acid;
- 10 2-(2-Benzoyl-phenylamino)-3-(4-{5-[4-(5-{4-[2-(2-benzoyl-phenylamino)-2-methoxycarbonyl-ethyl]-phenoxy]-pent-3-en-1-ynyl]-phenyl}-pent-2-en-4-ynyloxy)-phenyl)-propionic acid methyl ester;
- 2-(2-Benzoyl-phenylamino)-3-(4-{5-[4-(5-{4-[2-(2-benzoyl-phenylamino)-2-carboxy-ethyl]-phenoxy]-pent-3-en-1-ynyl]-phenyl}-pent-2-en-4-ynyloxy)-phenyl)-propionic acid;
- 15 2-Ethoxy-3-{4-[3-(4'-{3-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-1-methyl-propenyl}-biphenyl-4-yl)-but-2-enyloxy]-phenyl}-propionic acid ethyl ester;
- 3-{4-[3-(4'-{3-[4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy]-1-methyl-propenyl}-biphenyl-4-yl)-but-2-enyloxy]-phenyl}-2-ethoxy-propionic acid;
- 20 2-Ethoxy-3-{4-[5-(7-{5-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-3-methyl-pent-3-en-1-ynyl}-9-oxo-9H-fluoren-2-yl)-3-methyl-pent-2-en-4-ynyloxy]-phenyl}-propionic acid ethyl ester;
- 3-{4-[5-(7-{5-[4-(2-carboxy-2-ethoxy-ethyl)-phenoxy]-3-methyl-pent-3-en-1-ynyl}-9-oxo-9H-fluoren-2-yl)-3-methyl-pent-2-en-4-ynyloxy]-phenyl}-2-ethoxy-propionic acid;
- 25 [4-(3-{3-[3-(4-Methoxycarbonylmethyl-phenoxy)-prop-1-ynyl]-phenyl}-prop-2-ynyloxy)-phenyl]-acetic acid methyl ester;
- [4-(3-{3-[3-(4-Methoxycarbonylmethyl-phenoxy)-prop-1-ynyl]-phenyl}-prop-2-ynyloxy)-phenyl]-acetic acid;
- 30 [4-(5-{4-[5-(4-Methoxycarbonylmethoxy-3-methyl-phenoxy)-pent-3-en-1-ynyl]-phenyl}-pent-2-en-4-ynyloxy)-2-methyl-phenoxy]-acetic acid methyl ester;
- [4-(5-{4-[5-(4-Methoxycarbonylmethoxy-3-methyl-phenoxy)-pent-3-en-1-ynyl]-phenyl}-pent-2-en-4-ynyloxy)-2-methyl-phenoxy]-acetic acid;
- 35 3-{3-Bromo-4-[5-(4-{5-[2-bromo-4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-pent-3-en-1-ynyl]-phenyl}-pent-2-en-4-ynyloxy)-phenyl}-2-ethoxy-propionic acid ethyl ester;

- 3-{3-Bromo-4-[5-(4-{5-[2-bromo-4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-pent-3-en-1-ynyl}-phenyl)-pent-2-en-4-ynyloxy]-phenyl}-2-ethoxy-propionic acid;
- [3-(5-{4-[5-(3-Ethoxycarbonylmethyl-phenoxy)-pent-3-en-1-ynyl]-phenyl}-pent-2-en-4-ynyloxy)-phenyl]-acetic acid ethyl ester;
- 5 [3-(5-{4-[5-(3-Ethoxycarbonylmethyl-phenoxy)-pent-3-en-1-ynyl]-phenyl}-pent-2-en-4-ynyloxy)-phenyl]-acetic acid;
- 2-Ethoxy-3-{4-[5-(4'-[5-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-3-methyl-pent-3-en-1-ynyl]-biphenyl-4-yl)-3-methyl-pent-2-en-4-ynyloxy]-phenyl}-propionic acid ethyl ester;
- 2-Ethoxy-3-{4-[5-(4'-[5-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-3-methyl-pent-3-en-1-ynyl]-biphenyl-4-yl)-3-methyl-pent-2-en-4-ynyloxy]-phenyl}-propionic acid;
- 10 2-Ethoxy-3-{4-[5-(4-[5-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-3-methyl-pent-3-en-1-ynyl]-phenyl)-3-methyl-pent-2-en-4-ynyloxy]-phenyl}-propionic acid ethyl ester;
- 2-Ethoxy-3-{4-[5-(4-[5-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-3-methyl-pent-3-en-1-ynyl]-phenyl)-3-methyl-pent-2-en-4-ynyloxy]-phenyl}-propionic acid;
- 15 2-Ethoxy-3-{4-[5-(3-[5-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-3-methyl-pent-3-en-1-ynyl]-phenyl)-3-methyl-pent-2-en-4-ynyloxy]-phenyl}-propionic acid ethyl ester;
- 2-Ethoxy-3-{4-[5-(3-[5-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-3-methyl-pent-3-en-1-ynyl]-phenyl)-3-methyl-pent-2-en-4-ynyloxy]-phenyl}-propionic acid;
- [4-(3-{7-[3-(4-Methoxycarbonylmethoxy-3-methyl-phenylsulfanyl)-propenyl]-9H-fluoren-2-yl)-allylsulfanyl]-2-methyl-phenoxy]-acetic acid methyl ester; or
- 20 a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

Other examples of specific compounds of the invention are:

- 25 (4-(3-(4'-(3-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-propenyl)-biphenyl-4-yl)-allylsulfanyl)-2-methyl-phenoxy)-acetic acid;
- 3-(4-(3-(4'-(3-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-propenyl)-biphenyl-4-yl)-allylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- 3-(4-(3-(4'-(3-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-propenyl)-biphenyl-4-yl)-allyloxy)-phenyl)-2-ethoxy-propionic acid;
- 30 3-(4-(3-(4'-(3-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-propenyl)-biphenyl-4-yl)-allyloxy)-phenyl)-2-ethoxy-propionic acid;
- 3-(4-(3-(4'-(3-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-propenyl)-biphenyl-4-yl)-allylsulfanyl)-phenyl)-2-ethoxy-propionic acid;

- (4-(3-(4'-(3-(4-Carboxymethoxy-2-chloro-phenoxy)-propenyl)-biphenyl-4-yl)-allylsulfanyl)-2-methyl-phenoxy)-acetic acid;
- (4-(3-(4'-(3-(4-Carboxymethoxy-2-chloro-phenoxy)-propenyl)-biphenyl-4-yl)-allyloxy)-3-chloro-phenyl)-acetic acid;
- 5 3-(4-(3-(4'-(3-(4-Carboxymethoxy-2-chloro-phenoxy)-propenyl)-biphenyl-4-yl)-allyloxy)-phenyl)-2-ethoxy-propionic acid;
- 3-(4-(3-(4'-(3-(4-Carboxymethoxy-2-chloro-phenoxy)-propenyl)-biphenyl-4-yl)-allylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- 10 (4-(3-(7-(3-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-propenyl)-9H-fluoren-2-yl)-allylsulfanyl)-2-methyl-phenoxy)-acetic acid;
- 3-(4-(3-(7-(3-(4-carboxymethoxy-3-methyl-phenylsulfanyl)-propenyl)-9H-fluoren-2-yl)-allylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- 3-(4-(3-(7-(3-(4-carboxymethoxy-3-methyl-phenylsulfanyl)-propenyl)-9H-fluoren-2-yl)-allyloxy)-phenyl)-2-ethoxy-propionic acid;
- 15 (4-(3-(7-(3-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-propenyl)-9H-fluoren-2-yl)-allyloxy)-3-chloro-phenyl)-acetic acid;
- 3-(4-(3-(7-(3-(4-carboxymethoxy-2-chloro-phenoxy)-propenyl)-9H-fluoren-2-yl)-allylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- 20 3-(4-(3-(7-(3-(4-carboxymethoxy-2-chloro-phenoxy)-propenyl)-9H-fluoren-2-yl)-allyloxy)-phenyl)-2-ethoxy-propionic acid;
- 3-(4-(3-(7-(3-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-propenyl)-9H-fluoren-2-yl)-allyloxy)-phenyl)-2-ethoxy-propionic acid;
- 3-(4-(3-(7-(3-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-propenyl)-9H-fluoren-2-yl)-allylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- 25 (4-(3-(7-(3-(4-Carboxymethoxy-2-chloro-phenyxy)-propenyl)-9H-fluoren-2-yl)-allyloxy)-3-chloro-phenyl)-acetic acid;
- 3-(4-(3-(4'-(3-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-1-methyl-propenyl)-biphenyl-4-yl)-but-2-enyloxy)-phenyl)-2-ethoxy-propionic acid;
- 30 3-(4-(3-(4'-(3-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-1-methyl-propenyl)-biphenyl-4-yl)-but-2-enylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- (4-(3-(4'-(3-(4-Carboxymethyl-2-chloro-phenoxy)-1-methyl-propenyl)-biphenyl-4-yl)-but-2-enyloxy)-3-chloro-phenyl)-acetic acid;

- (4-(3-(4'-(3-(4-Carboxymethyl-3-methyl-phenylsulfanyl)-1-methyl-propenyl)-biphenyl-4-yl)-but-2-enylsulfanyl)-2-methyl-phenoxy)-acetic acid;
- 3-(4-(3-(4'-(3-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-1-methyl-propenyl)-biphenyl-4-yl)-but-2-enylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- 5 3-(4-(3-(4'-(3-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-1-methyl-propenyl)-biphenyl-4-yl)-but-2-enyloxy)-phenyl)-2-ethoxy-propionic acid;
- 3-(4-(3-(4'-(3-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-1-methyl-propenyl)-biphenyl-4-yl)-but-2-enyloxy)-phenyl)-2-ethoxy-propionic acid;
- 10 3-(4-(5-(4-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
- 3-(4-(5-(4-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- 4-(5-(4-(5-(4-Carboxymethyl-2-chloro-phenoxy)-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynyloxy)-3-chloro-phenyl)-acetic acid;
- 15 4-(5-(4-(5-(4-Carboxymethyl-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynylsulfanyl)-2-methyl-phenoxy)-acetic acid;
- 3-(4-(5-(4-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- 20 3-(4-(5-(4-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
- 3-(4-(5-(4'-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-pent-3-en-1-ynyl)-biphenyl-4-yl)-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
- 25 3-(4-(5-(4'-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-pent-3-en-1-ynyl)-biphenyl-4-yl)-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- 4-(5-(4'-(5-(4-Carboxymethyl-2-chloro-phenoxy)-pent-3-en-1-ynyl)-biphenyl-4-yl)-pent-2-en-4-ynyloxy)-3-chloro-phenyl)-acetic acid;
- 4-(5-(4'-(5-(4-Carboxymethyl-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)-biphenyl-4-yl)-pent-2-en-4-ynylsulfanyl)-2-methyl-phenoxy)-acetic acid;
- 30 3-(4-(5-(4'-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)-biphenyl-4-yl)-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- 3-(4-(5-(4'-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)-biphenyl-4-yl)-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;

- (4-(5-(4'-(5-(4-Carboxymethyl-2-chloro-phenoxy)-3-methyl-pent-3-en-1-ynyl)-biphenyl-4-yl)-3-methyl-pent-2-en-4-ynyloxy)-3-chloro-phenyl)-acetic acid;
- (4-(5-(4'-(5-(4-Carboxymethyl-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-biphenyl-4-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-2-methyl-phenoxy)-acetic acid;
- 5 3-(4-(5-(4'-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-3-methyl-pent-3-en-1-ynyl)-biphenyl-4-yl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl-2-ethoxy-propionic acid;
- 3-(4-(5-(4'-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-biphenyl-4-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-phenyl-2-ethoxy-propionic acid;
- 10 3-(4-(5-(4'-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-biphenyl-4-yl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl-2-ethoxy-propionic acid;
- 3-(4-(5-(4'-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-biphenyl-4-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-phenyl-2-ethoxy-propionic acid;
- 3-(4-(5-(4'-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-biphenyl-4-yl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl-2-ethoxy-propionic acid;
- 15 (4-(5-(4''-(5-(4-Carboxymethyl-2-chloro-phenoxy)-3-methyl-pent-3-en-1-ynyl)-[1,1';4'1'']terphenyl-4-yl)-3-methyl-pent-2-en-4-ynyloxy)-3-chloro-phenyl)-acetic acid;
- (4-(5-(4''-(5-(4-Carboxymethyl-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-[1,1';4'1'']terphenyl-4-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-2-methyl-phenoxy)-acetic acid;
- 20 3-(4-(5-(4''-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-3-methyl-pent-3-en-1-ynyl)-[1,1';4'1'']terphenyl-4-yl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl-2-ethoxy-propionic acid;
- 3-(4-(5-(4''-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-[1,1';4'1'']terphenyl-4-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-phenyl-2-ethoxy-propionic acid;
- 3-(4-(5-(4''-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-[1,1';4'1'']terphenyl-4-yl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl-2-ethoxy-propionic acid;
- 25 3-(4-(5-(4''-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-[1,1';4'1'']terphenyl-4-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-phenyl-2-ethoxy-propionic acid;
- 3-(4-(5-(4''-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-[1,1';4'1'']terphenyl-4-yl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl-2-ethoxy-propionic acid;
- 30 3-(4-(5-(4''-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-pent-3-en-1-ynyl)-[1,1';4'1'']terphenyl-4-yl)-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
- 3-(4-(5-(4''-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-pent-3-en-1-ynyl)-[1,1';4'1'']terphenyl-4-yl)-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;

- 4-(5-(4''-(5-(4-Carboxymethyl-2-chloro-phenoxy)-pent-3-en-1-ynyl)-[1,1';4'1'']terphenyl-4-yl)-pent-2-en-4-ynyloxy)-3-chloro-phenyl)-acetic acid;
- 4-(5-(4''-(5-(4-Carboxymethyl-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)-[1,1';4'1'']terphenyl-4-yl)-pent-2-en-4-ynylsulfanyl)-2-methyl-phenoxy)-acetic acid;
- 5 3-(4-(5-(4''-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)-[1,1';4'1'']terphenyl-4-yl)-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- 3-(4-(5-(4''-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)-[1,1';4'1'']terphenyl-4-yl)-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
- 10 (4-(5-(4-(5-(4-Carboxymethyl-2-chloro-phenoxy)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynyloxy)-3-chloro-phenyl)-acetic acid;
- (4-(5-(4-(5-(4-Carboxymethyl-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynylsulfanyl)-2-methyl-phenoxy)-acetic acid;
- 3-(4-(5-(4-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
- 15 3-(4-(5-(4-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- 3-(4-(5-(4-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
- 20 3-(4-(5-(4-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- 3-(4-(5-(4-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
- 25 3-(4-(5-(3-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
- 3-(4-(5-(3-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- 4-(5-(3-(5-(4-Carboxymethyl-2-chloro-phenoxy)-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynyloxy)-3-chloro-phenyl)-acetic acid;
- 30 4-(5-(3-(5-(4-Carboxymethyl-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynylsulfanyl)-2-methyl-phenoxy)-acetic acid;
- 3-(4-(5-(3-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;

3-(4-(5-(3-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;

- 5 (4-(5-(3-(5-(4-Carboxymethyl-2-chloro-phenoxy)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynyloxy)-3-chloro-phenyl)-acetic acid;
 (4-(5-(3-(5-(4-Carboxymethyl-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynylsulfanyl)-2-methyl-phenoxy)-acetic acid;
 3-(4-(5-(3-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
- 10 3-(4-(5-(3-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
 3-(4-(5-(3-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
- 15 3-(4-(5-(3-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
 3-(4-(5-(3-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
- 20 3-(4-(5-(7-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-3-methyl-pent-3-en-1-ynyl)-9-oxo-9H-fluoren-2-yl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
 3-(4-(5-(7-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-9-oxo-9H-fluoren-2-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
 (4-(5-(7-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-9-oxo-9H-fluoren-2-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-2-methyl-phenoxy)- acetic acid;
- 25 3-(4-(5-(7-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-3-methyl-pent-3-en-1-ynyl)-9H-fluoren-2-yl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
 3-(4-(5-(7-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-9H-fluoren-2-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- 30 (4-(5-(7-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-9H-fluoren-2-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-2-methyl-phenoxy)- acetic acid;
- 35 3-(4-(5-(7-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-pent-3-en-1-ynyl)-9-oxo-9H-fluoren-2-yl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;

- 3-(4-(5-(7-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phensulfanyl-pent-3-en-1-ynyl)-9-oxo-9*H*-fluoren-2-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
 (4-(5-(7-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl-pent-3-en-1-ynyl)-9-oxo-9*H*-fluoren-2-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-2-methyl-phenoxy)- acetic acid;
- 5 3-(4-(5-(7-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy-pent-3-en-1-ynyl)-9*H*-fluoren-2-yl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
 3-(4-(5-(7-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phensulfanyl-pent-3-en-1-ynyl)- 9*H*-fluoren-2-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- 10 (4-(5-(7-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)- 9*H*-fluoren-2-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-2-methyl-phenoxy)- acetic acid;
- 3-(4-(5-(7-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-3-methyl-pent-3-en-1-ynyl)-9*H*-carbazol-2-yl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
- 15 3-(4-(5-(7-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phensulfanyl)-3-methyl-pent-3-en-1-ynyl)- 9*H*-carbazol-2-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
 (4-(5-(7-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)- 9*H*-carbazol-2-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-2-methyl-phenoxy)- acetic acid;
- 20 3-(4-(5-(7-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy-pent-3-en-1-ynyl)-9*H*-fluoren-2-yl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
 3-(4-(5-(7-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phensulfanyl-pent-3-en-1-ynyl)- 9*H*- carbazol-2-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
 (4-(5-(7-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)- 9*H*- carbazol-2-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-2-methyl-phenoxy)- acetic acid, or
- 25 a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

The present invention also encompasses pharmaceutically acceptable salts of the present compounds. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable base addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, nitric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic,

propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methanesulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids, sulphates, nitrates, phosphates, perchlorates, borates, acetates, benzoates, hydroxynaphthoates, glycerophosphates, ketoglutarates and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977, 66, 2, which is incorporated herein by reference. Examples of metal salts include lithium, sodium, potassium, magnesium, zinc, calcium salts and the like. Examples of amines and organic amines include ammonium, methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, propylamine, butylamine, tetramethylamine, ethanolamine, diethanolamine, triethanolamine, meglumine, ethylenediamine, choline, N,N'-dibenzylethylenediamine, N-benzylphenylethylamine, N-methyl-D-glucamine, guanidine and the like. Examples of cationic amino acids include lysine, arginine, histidine and the like.

The pharmaceutically acceptable salts are prepared by reacting the present compound with 1 to 4 equivalents of a base such as sodium hydroxide, sodium methoxide, sodium hydride, potassium t-butoxide, calcium hydroxide, magnesium hydroxide and the like, in solvents like ether, THF, methanol, t-butanol, dioxane, isopropanol, ethanol etc. Mixture of solvents may be used. Organic bases like lysine, arginine, diethanolamine, choline, guanidine and their derivatives etc. may also be used. Alternatively, acid addition salts wherever applicable are prepared by treatment with acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, p-toluenesulphonic acid, methanesulfonic acid, acetic acid, citric acid, maleic acid, salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzenesulfonic acid, tartaric acid and the like in solvents like ethyl acetate, ether, alcohols, acetone, THF, dioxane etc. Mixture of solvents may also be used.

The stereoisomers of the compounds forming part of this invention may be prepared by using reactants in their single enantiomeric form in the process wherever possible or by conducting the reaction in the presence of reagents or catalysts in their single enantiomer form or by resolving the mixture of stereoisomers by conventional methods. Some of the preferred methods include use of microbial resolution, enzymatic resolution, resolving the diastereomeric salts formed with chiral acids such as mandelic acid, camphorsulfonic acid, tartaric acid, lactic acid, and the like wherever applicable or chiral bases such as brucine, (R)- or (S)-phenylethylamine, cinchona alkaloids and their derivatives and the like. Com-

monly used methods are compiled by Jaques et al in "Enantiomers, Racemates and Resolution" (Wiley Interscience, 1981). More specifically the present compound may be converted to a 1:1 mixture of diastereomeric amides by treating with chiral amines, aminoacids, aminoalcohols derived from aminoacids; conventional reaction conditions may be employed to
5 convert acid into an amide; the diastereomers may be separated either by fractional crystallization or chromatography and the stereoisomers of the compound of the present invention may be prepared by hydrolysing the pure diastereomeric amide.

Various polymorphs of compound of the present invention forming part of this invention may be prepared by crystallization of compound of the invention under different conditions. For example, using different solvents commonly used or their mixtures for recrystalliza-
10 tion; crystallizations at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe nmr spectroscopy, ir spectroscopy, differential scanning
15 calorimetry, powder X-ray diffraction or such other techniques.

The invention also encompasses prodrugs of the present compounds, which on administration undergo chemical conversion by metabolic processes before becoming active pharmacological substances. In general, such prodrugs will be functional derivatives of the present compounds, which are readily convertible in vivo into the required compound of the
20 the present invention. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The invention also encompasses active metabolites of the present compounds.

The invention also relates to pharmaceutical compositions comprising, as an active
25 ingredient, at least one compound of the the present invention or any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable carriers or diluents.

Furthermore, the invention relates to the use of compounds of the present invention or their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts or pharmaceutically acceptable solvates thereof for the preparation of a pharmaceutical composition for the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR) such as the conditions mentioned above.
30

In another aspect, the present invention relates to a method of treating and/or
35 preventing Type I or Type II diabetes.

In a still further aspect, the present invention relates to the use of one or more compounds of the present invention or pharmaceutically acceptable salts thereof for the preparation of a pharmaceutical composition for the treatment and/or prevention of Type I or Type II diabetes.

5 In a still further aspect, the present compounds are useful for the treatment and/or prevention of IGT.

In a still further aspect, the present compounds are useful for the treatment and/or prevention of Type 2 diabetes.

10 In a still further aspect, the present compounds are useful for the delaying or prevention of the progression from IGT to Type 2 diabetes.

In a still further aspect, the present compounds are useful for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.

15 In another aspect, the present compounds reduce blood glucose and triglyceride levels and are accordingly useful for the treatment and/or prevention of ailments and disorders such as diabetes and/or obesity.

20 In still another aspect, the present compounds are useful for the treatment and/or prophylaxis of insulin resistance (Type 2 diabetes), impaired glucose tolerance, dyslipidemia, disorders related to Syndrome X such as hypertension, obesity, insulin resistance, hyperglycaemia, atherosclerosis, hyperlipidemia, coronary artery disease, myocardial ischemia and other cardiovascular disorders.

In still another aspect, the present compounds are effective in decreasing apoptosis in mammalian cells such as beta cells of Islets of Langerhans.

25 In still another aspect, the present compounds are useful for the treatment of certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis.

In still another aspect, the present compounds may also be useful for improving cognitive functions in dementia, treating diabetic complications, psoriasis, polycystic ovarian syndrome (PCOS) and prevention and treatment of bone loss, e.g. osteoporosis.

30 The present compounds may also be administered in combination with one or more further pharmacologically active substances eg., selected from antiobesity agents, antidiabetics, antihypertensive agents, agents for the treatment and/or prevention of complications resulting from or associated with diabetes and agents for the treatment and/or prevention of complications and disorders resulting from or associated with obesity.

Thus, in a further aspect of the invention the present compounds may be administered in combination with one or more antiobesity agents or appetite regulating agents.

Such agents may be selected from the group consisting of CART (cocaine amphetamine regulated transcript) agonists, NPY (neuropeptide Y) antagonists, MC4 (melanocortin 4) agonists, orexin antagonists, TNF (tumor necrosis factor) agonists, CRF (corticotropin releasing factor) agonists, CRF BP (corticotropin releasing factor binding protein) antagonists, urocortin agonists, $\beta 3$ agonists, MSH (melanocyte-stimulating hormone) agonists, MCH (melanocyte-concentrating hormone) antagonists, CCK (cholecystokinin) agonists, serotonin re-uptake inhibitors, serotonin and noradrenaline re-uptake inhibitors, mixed serotonin and noradrenergic compounds, 5HT (serotonin) agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone releasing compounds, TRH (thyrotropin releasing hormone) agonists, UCP 2 or 3 (uncoupling protein 2 or 3) modulators, leptin agonists, DA agonists (bromocriptin, doprexin), lipase/amylase inhibitors, RXR (retinoid X receptor) modulators or TR β agonists.

15 In one embodiment of the invention the antiobesity agent is leptin.

In another embodiment the antiobesity agent is dexamphetamine or amphetamine.

In another embodiment the antiobesity agent is fenfluramine or dexfenfluramine.

In still another embodiment the antiobesity agent is sibutramine.

In a further embodiment the antiobesity agent is orlistat.

20 In another embodiment the antiobesity agent is mazindol or phentermine.

Suitable antidiabetics comprise insulin, GLP-1 (glucagon like peptide-1) derivatives such as those disclosed in WO 98/08871 to Novo Nordisk A/S, which is incorporated herein by reference as well as orally active hypoglycaemic agents.

The orally active hypoglycaemic agents preferably comprise sulphonylureas, biguanides, meglitinides, glucosidase inhibitors, glucagon antagonists such as those disclosed in
25 WO 99/01423 to Novo Nordisk A/S and Agouron Pharmaceuticals, Inc., GLP-1 agonists, potassium channel openers such as those disclosed in WO 97/26265 and WO 99/03861 to Novo Nordisk A/S which are incorporated herein by reference, DPP-IV (dipeptidyl peptidase-IV) inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis and/or
30 glycogenolysis, glucose uptake modulators, compounds modifying the lipid metabolism such as antihyperlipidemic agents and antilipidemic agents as HMG CoA inhibitors (statins), compounds lowering food intake, RXR agonists and agents acting on the ATP-dependent potassium channel of the β -cells.

In one embodiment of the invention the present compounds are administered in
35 combination with insulin.

In a further embodiment the present compounds are administered in combination with a sulphonylurea eg. tolbutamide, glibenclamide, glipizide or glicazide.

In another embodiment the present compounds are administered in combination with a biguanide eg. metformin.

5 In yet another embodiment the present compounds are administered in combination with a meglitinide eg. repaglinide or senaglinide.

In a further embodiment the present compounds are administered in combination with an α -glucosidase inhibitor eg. miglitol or acarbose.

10 In another embodiment the present compounds are administered in combination with an agent acting on the ATP-dependent potassium channel of the β -cells eg. tolbutamide, glibenclamide, glipizide, glicazide or repaglinide.

Furthermore, the present compounds may be administered in combination with nateglinide.

15 In still another embodiment the present compounds are administered in combination with an antihyperlipidemic agent or antilipidemic agent eg. cholestyramine, colestipol, clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, probucol or dextrothyroxine.

20 In a further embodiment the present compounds are administered in combination with more than one of the above-mentioned compounds eg. in combination with a sulphonylurea and metformin, a sulphonylurea and acarbose, repaglinide and metformin, insulin and a sulphonylurea, insulin and metformin, insulin, insulin and lovastatin, etc.

25 Furthermore, the present compounds may be administered in combination with one or more antihypertensive agents. Examples of antihypertensive agents are β -blockers such as alprenolol, atenolol, timolol, pindolol, propranolol and metoprolol, ACE (angiotensin converting enzyme) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril and ramipril, calcium channel blockers such as nifedipine, felodipine, nifedipine, isradipine, nimodipine, diltiazem and verapamil, and α -blockers such as doxazosin, urapidil, prazosin and terazosin. Further reference can be made to Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

30 It should be understood that any suitable combination of the compounds according to the invention with one or more of the above-mentioned compounds and optionally one or more further pharmacologically active substances are considered to be within the scope of the present invention.

The present invention also relates to a process for the preparation of the above said novel compounds, their derivatives, their analogs, their tautomeric forms, their stereoisom-

ers, their polymorphs, their pharmaceutically acceptable salts or pharmaceutically acceptable solvates.

PHARMACEUTICAL COMPOSITIONS

The compounds of the invention may be administered alone or in combination with
5 pharmaceutically acceptable carriers or excipients, in either single or multiple doses. The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co.,
10 Easton, PA, 1995. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

Typical compositions include a compound of the present invention or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or
15 enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves
20 as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatine, lactose, terra alba, sucrose, cyclodextrin, amylose, magnesium stearate, talc,
25 gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also
30 include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical compositions can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteriously react with the active compounds.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

If a solid carrier is used for oral administration, the preparation may be tableted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

For nasal administration, the preparation may contain a compound of the invention dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet which may be prepared by conventional tableting techniques may contain:

Core:

Active compound (as free compound or salt thereof)	5 mg
Colloidal silicon dioxide (Aerosil)	1.5 mg
Cellulose, microcryst. (Avicel)	70 mg
Modified cellulose gum (Ac-Di-Sol)	7.5 mg
Magnesium stearate	Ad.

Coating:

HPMC approx.	9 mg
--------------	------

*Mywacett 9-40 T approx.

0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

5 If desired, the pharmaceutical composition of the invention may comprise the compound of the present invention in combination with further pharmacologically active substances such as those described in the foregoing.

 The compounds of the invention may be administered to a mammal, especially a human in need of such treatment, prevention, elimination, alleviation or amelioration of
10 diseases related to the regulation of blood sugar.

 Such mammals include also animals, both domestic animals, e.g. household pets, and non-domestic animals such as wildlife.

 The compounds of the invention are effective over a wide dosage range. A typical oral dosage is in the range of from about 0.001 to about 100 mg/kg body weight per day,
15 preferably from about 0.01 to about 50 mg/kg body weight per day, and more preferred from about 0.05 to about 10 mg/kg body weight per day administered in one or more dosages such as 1 to 3 dosages. The exact dosage will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated and other factors evident to those skilled in the art.
20

 The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art. A typical unit dosage form for oral administration one or more times per day such as 1 to 3 times per day may contain of from 0.05 to about 1000 mg, preferably from about 0.1 to about 500 mg, and more preferred from about 0.5 mg to about
25 200 mg.

 Any novel feature or combination of features described herein is considered essential to this invention.

 The present invention is further illustrated in the following representative examples which are, however, not intended to limit the scope of the invention in any way.

30 **EXAMPLES**

 The compounds used as starting materials are either known compounds or compounds which can readily be prepared by methods known per se. The structures of the compounds are confirmed by either elemental analysis (MA), nuclear magnetic resonance (NMR, 300 MHz), mass spectrometry (MS) or optical rotation. NMR shifts (δ) are given in parts per

million (ppm) and only selected peaks are given. Mp is melting point and is given in °C. Column chromatography was carried out using the technique described by W.C. Still et al, J. Org. Chem. 1978, 43, 2923-2925 on Merck silica gel 60 (Art 9385).

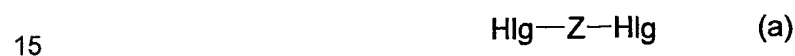
The abbreviations as used in the examples have the following meaning:

- 5 THF: tetrahydrofuran
 DMSO: dimethylsulfoxide
 CDCl₃: deuterated chloroform
 DMF: N,N-dimethylformamide
 min: minutes
 10 h: hours

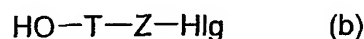
General procedure (A)

Step A:

Reacting a compound of formula (a)



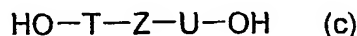
wherein Z is defined as above and wherein Hlg is chlorine, bromine or iodine, with a appropriate compound of formula T-OH wherein T is defined as above, through a crosscoupling reaction employing a Pd catalyst such as Pd(PPh₃)₂ or PdCl₂(PPh₃)₂ and a catalytic amount
 20 of in example copper(I)iodide and an organic amine base, such as and if needed a cosolvent to give a compound of formula (b)



25 wherein Z and T are defined as above and wherein Hlg is chlorine, bromine or iodine.

Step B:

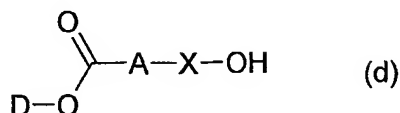
Reacting a compound of formula (b) wherein Z and T are defined as above and wherein Hlg is chlorine, bromine or iodine, with a appropriate compound of formula U-OH wherein U is defined as above, through a crosscoupling reaction employing a Pd catalyst
 30 such as Pd(PPh₃)₂ or PdCl₂(PPh₃)₂ and a catalytic amount of in example copper(I)iodide and an organic amine base, such as and if needed a cosolvent to give a compound of formula (c)



wherein Z, T and U are defined as above.

Step C:

- 5 Reacting a compound of formula (c), wherein T, Z and U are defined as above, with
a compound of formula (d)

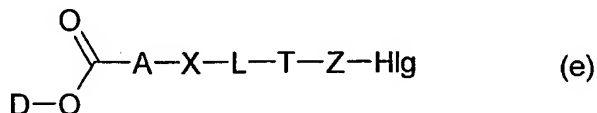


- 10 wherein A, X and D are defined as above except that D is not hydrogen, under Mitsunobu
conditions, using a reagent such as triphenylphosphine/diethylazodicarboxylate and the like,
to obtain a compound of formula (I), wherein A, B, D, E, L, M, T, U, X, Y and Z are defined as
above, except that D and E is not hydrogen, and wherein A and B are identical and wherein
X and Y are identical, and wherein L and M is oxygen.

General procedure (B)

15 Step A:

- Reacting a compound of formula (b), wherein T and Z are defined as above and
wherein Hlg is chlorine, bromine or iodine, with a compound of formula (d), wherein A, X and
D are defined as above except that D is not hydrogen, under Mitsunobu conditions, using a
reagent such as triphenylphosphine/diethylazodicarboxylate and the like to obtain a com-
20 pound of formula (e)

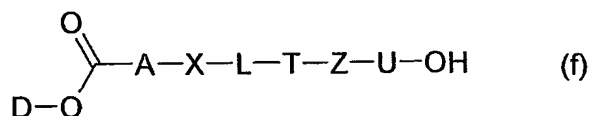


- 25 wherein A, D, T, X and Z are defined as above except that D is not hydrogen and wherein
Hlg is chlorine, bromine and iodine, and wherein L is oxygen.

Step B:

Reacting a compound of formula (e), wherein A, D, T, X and Z is defined as above,
and wherein Hlg is chlorine, bromine or iodine, and wherein L is oxygen, with a appropriate
compound of formula U-OH wherein U is defined as above, through a crosscoupling reaction

employing a Pd catalyst such as $\text{Pd}(\text{PPh}_3)_2$ or $\text{PdCl}_2(\text{PPh}_3)_2$ and a catalytic amount of in example copper(I)iodide and an organic amine base, such as and if needed a cosolvent to give a compound of formula (f)



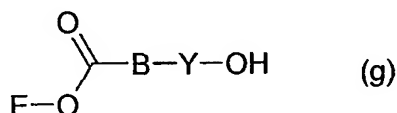
5

wherein A, D, T, U, X and Z are defined as above, and wherein L is oxygen.

Step C:

Reacting the compound of formula (f), wherein A, D, T, U, X and Z are defined as above, except that D is not hydrogen, and wherein L is oxygen with a compound of formula (g)

10



15

wherein B, E and Y are defined as above except that E is not hydrogen, under Mitsunobu conditions, using a reagent such as triphenylphosphine/diethylazodicarboxylate and the like, to obtain a compound of formula (I), wherein A, B, D, E, L, M, T, U, X, Y and Z are defined as above, except that D and E is not hydrogen, and wherein L and M is oxygen.

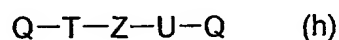
General procedure (C)

Step A:

20

Converting the -OH functionality in the compound of formula (c), wherein T, Z and U are defined as above, to an appropriate leaving group (Q) such as p-toluenesulfonate, methanesulfonate, halogen (for example by methods according to: Houben-Weyl, Methoden der organischen Chemie, Alkohole III, 6/1b, Thieme-Verlag 1984, 4th Ed., pp. 927-939; Comprehensive Organic Transformations. A guide to functional group preparations, VCH Publishers 1989, 1st Ed., pp. 353-363 and *J. Org. Chem.*, Vol. 36 (20), 3044-3045, 1971), triflate and the like, to give a compound of formula (h)

25



wherein Q, T, U and Z are defined as above.

Step B:

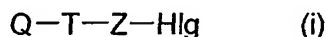
Reacting the compound of formula (h) wherein Q is a leaving group such as p-toluenesulfonate, methanesulfonate, halogen, triflate and the like and wherein T, U and Z are defined as above with a compound of formula (d), wherein A, X and D are defined as above except that D is not hydrogen, to give a compound of formula (I) wherein A, B, D, E, L, M, T, U, X, Y and Z are defined as above, except that D and E is not hydrogen, and wherein A and B are identical and wherein X and Y are identical.

General procedure (D)

10 Step A:

Converting the -OH functionality in the compound of formula (b), wherein T and Z are defined as above, and wherein Hlg is chlorine, bromine and iodine, to an appropriate leaving group (Q) such as p-toluenesulfonate, methanesulfonate, halogen (for example by methods according to: Houben-Weyl, Methoden der organischen Chemie, Alkohole III, 6/1b, Thieme-Verlag 1984, 4th Ed., pp. 927-939; Comprehensive Organic Transformations. A guide to functional group preparations, VCH Publishers 1989, 1st Ed., pp. 353-363 and J. Org. Chem., Vol. 36 (20), 3044-3045, 1971), triflate and the like, to give a compound of formula (i)

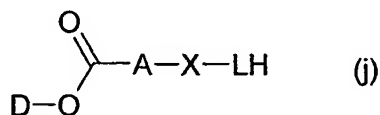
20



wherein Q, T and Z are defined as above, and wherein Hlg is chlorine, bromine or iodine.

Step B:

25 Reacting the compound of formula (i) wherein Q is a leaving group such as p-toluenesulfonate, methanesulfonate, halogen, triflate and the like and wherein T and Z are defined as above with a compound of formula (j)



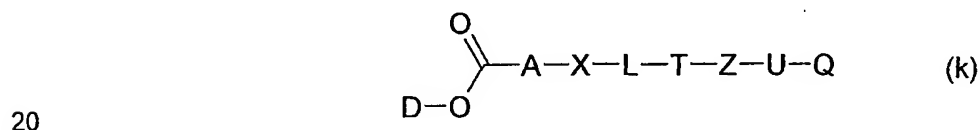
wherein A, X, D and L are defined as above except that D is not hydrogen, to give a compound of formula (e) wherein A, D, L, T, X and Z are defined as above except that D is not hydrogen and wherein Hlg is chlorine, bromine and iodine.

Step C:

- 5 Reacting a compound of formula (e), wherein A, D, L, T, X and Z is defined as above, and wherein Hlg is chlorine, bromine or iodine, with a appropriate compound of formula U-OH wherein U is defined as above, through a crosscoupling reaction employing a Pd catalyst such as $\text{Pd}(\text{PPh}_3)_2$ or $\text{PdCl}_2(\text{PPh}_3)_2$ and a catalytic amount of in example copper(I)iodide and an organic amine base, such as and if needed a cosolvent to give a compound of formula (f)
- 10 wherein A, D, L, T, U, X and Z are defined as above.

Step D:

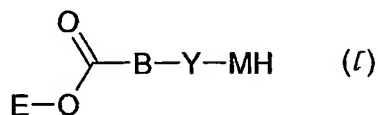
- Converting the -OH functionality in the compound of formula (f), wherein A, D, L, T, U, X and Z are defined as above, to an appropriate leaving group (Q) such as p-toluenesulfonate, methanesulfonate, halogen (for example by methods according to: Houben-Weyl,
- 15 Methoden der organischen Chemie, Alkohole III, 6/1b, Thieme-Verlag 1984, 4th Ed., pp. 927-939; Comprehensive Organic Transformations. A guide to functional group preparations, VCH Publishers 1989, 1st Ed., pp. 353-363 and *J. Org. Chem.*, Vol. 36 (20), 3044-3045, 1971), triflate and the like, to give a compound of formula (k)



wherein A, D, L, T, U, Q, X and Z are defined as above.

Step E:

- 25 Reacting the compound of formula (k) wherein Q is a leaving group such as p-toluenesulfonate, methanesulfonate, halogen, triflate and the like and wherein A; D, L, T, U, X and Z are defined as above with a compound of formula (l)



wherein B, E, M and Y are defined as above except that E is not hydrogen, to give a compound of formula (I) wherein A, B, D, E, L, M, T, U, X, Y and Z are defined as above, except that D and E is not hydrogen.

General procedure (E)

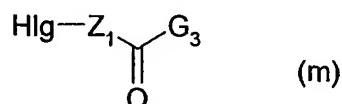
5 Step A:

By chemical or enzymatic saponification of a compound of formula (I) wherein A, B, D, E, L, M, T, U, X, Y and Z are defined as above, except that D and E are not hydrogen, to give a compound of formula (I) wherein A, B, L, M, T, U, X, Y and Z are defined as above, and wherein D and E is hydrogen.

10 **General procedure (F)**

Step A:

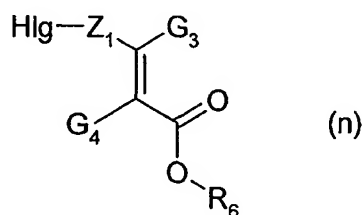
Reacting a compound of formula (m)



15

wherein Z_1 taken together with Z_2 form a divalent polycyclic ringsystem as defined for Z above, and wherein Hlg is chlorine, bromine or iodine and wherein G_3 is defined as above, through a Wittig-like process with for example $(\text{EtO})_2\text{PO}(\text{CHG}_4)\text{COOR}_6$ (wherein R_6 is an C_{1-3} -alkyl group and wherein G_4 is defined as above), in the presence of a base such as sodium hydride, EtONa and the like to give a compound of formula (n)

20



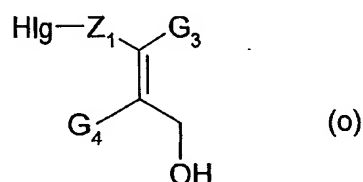
wherein R_6 is defined as above and wherein Z_1 taken together with Z_2 form a divalent polycyclic ringsystem as defined for Z above, and wherein Hlg is chlorine, bromine or iodine and wherein G_3 and G_4 are defined as above.

25

Step B:

Reducing the compound of formula (n), wherein R_6 is defined as above and wherein Z_1 taken together with Z_2 form a divalent polycyclic ringsystem as defined for Z above, and wherein Hlg is chlorine, bromine or iodine and wherein G_3 and G_4 are defined as above with a suitable

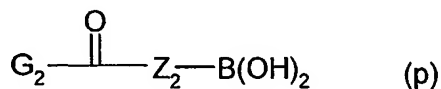
5 reagent such as diisobutylaluminium hydride, to give a compound of formula (o)



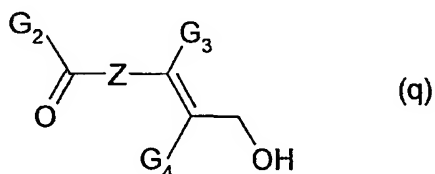
wherein Z_1 taken together with Z_2 form a divalent polycyclic ringsystem as defined for Z above, and wherein Hlg is chlorine, bromine or iodine and wherein G_3 and G_4 are defined as above.

Step C:

Reacting the compound of formula (o), wherein G_3 and G_4 are defined as above and wherein Z_1 taken together with Z_2 form a divalent polycyclic ringsystem as defined for Z above, and wherein Hlg is chlorine, bromine or iodine with a appropriate boronic acid of formula (p)



wherein Z_2 taken together with Z_1 form a divalent polycyclic ringsystem as defined for Z above, and G_2 is defined as above, to give a compound of formula (q)

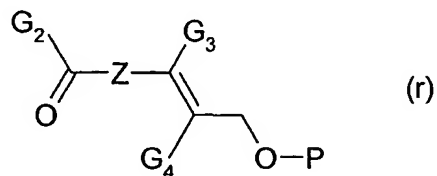


wherein Z, G_2 , G_3 and G_4 are defined as above.

Step D:

Protecting the -OH functionality in a compound of formula (q) wherein Z, G₂, G₃ and G₄ are defined as above, with an appropriate protecting group such as *tert*-butyldimethylsilyl to give a compound of formula (r)

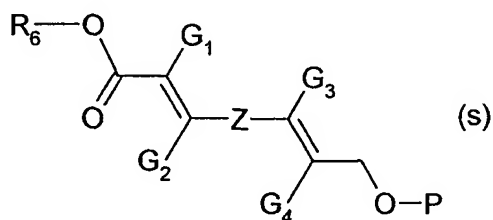
5



wherein Z, G₂, G₃ and G₄ are defined as above and wherein P is an appropriate protecting group such as *tert*-butyldimethylsilyl.

10 Step E:

Reacting the compound of formula (r), wherein Z, G₂, G₃ and G₄ are defined as above and wherein P is an appropriate protecting group such as *tert*-butyldimethylsilyl, through a Wittig-like process with for example (EtO)₂PO(CHG₁)COOR₆ (wherein R₆ is an C₁₋₃-alkyl group and wherein G₁ is defined as above), in the presence of a base such as sodium
15 hydride, EtONa and the like to give a compound of formula (s)

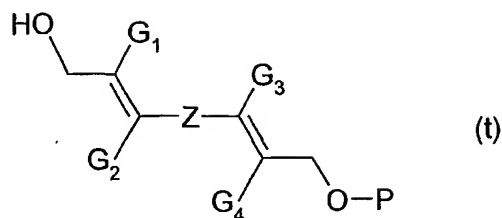


wherein Z, G₁, G₂, G₃ and G₄ is defined as above and wherein P is an appropriate protecting
20 group such as *tert*-butyldimethylsilyl and wherein R₆ is an C₁₋₃-alkyl group.

Step F:

Reducing the compound of formula (s), wherein Z, G₁, G₂, G₃ and G₄ are defined as above and wherein P is an appropriate protecting group such as *tert*-butyldimethylsilyl and wherein R₆ is an C₁₋₃-alkyl group, with a suitable reagent such as diisobutylaluminium hy-
25 dride, to give a compound of formula (t)

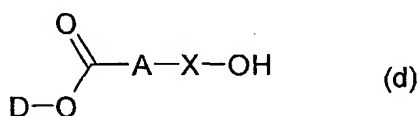
45



wherein Z, G₁, G₂, G₃ and G₄ are defined as above and wherein P is an appropriate protecting group such as *tert*-butyldimethylsilyl.

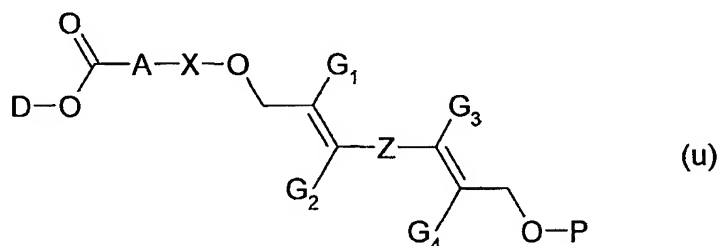
5 Step G:

Reacting a compound of formula (t) wherein Z, G₁, G₂, G₃ and G₄ are defined as above and wherein P is an appropriate protecting group such as *tert*-butyldimethylsilyl with a compound of formula (d)



10

wherein D, A and X are defined as above under Mitsunobu conditions, using a reagent such as triphenylphosphine/diethylazodicarboxylate and the like to obtain a compound of formula (u)



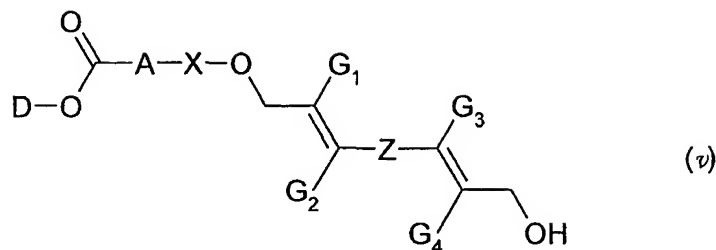
15

wherein A, D, X, Z, G₁, G₂, G₃ and G₄ are defined as above and wherein P is an appropriate protecting group such as *tert*-butyldimethylsilyl.

Step H:

Deprotecting a compound of formula (u) wherein A, D, X, Z, G₁, G₂, G₃ and G₄ are defined as above and wherein P is an appropriate protecting group such as *tert*-butyldimethylsilyl to give a compound of formula (v)

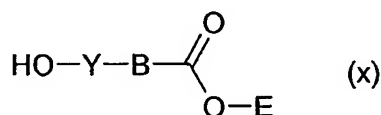
20



wherein A, D, X, Z, G₁, G₂, G₃ and G₄ are defined as above.

Step I:

- 5 Reacting a compound of formula (v) wherein A, D, X, Z, G₁, G₂, G₃ and G₄ are defined as above, with a compound of formula (x)

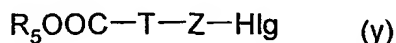


- 10 wherein Y, B and E are defined as above under Mitsunobu conditions, using a reagent such as triphenylphosphine/diethylazodicarboxylate and the like to obtain a compound of formula (I) wherein A, B, D, E, X, Y and Z are defined as above, except that D and E is not hydrogen and wherein L and M is oxygen and wherein T is -CH₂(CG₁)=(CG₂)- and wherein U is -CH₂(CG₃)=(CG₄)-.

15 **General procedure (G)**

Step A:

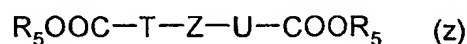
- Reacting a compound of formula (a) wherein Z is defined as above and wherein Hlg is chlorine, bromine or iodine, with a appropriate compound of formula T-COOR₅ wherein T is defined as above and R₅ is C₁₋₆-alkyl, through a crosscoupling reaction employing a Pd catalyst such as Pd(PPh₃)₂ or PdCl₂(PPh₃)₂ and a catalytic amount of in example copper(I)iodide and an organic amine base, such as and if needed a cosolvent to give a compound of formula (y)
- 20



wherein Z and T are defined as above and wherein Hlg is chlorine, bromine or iodine and wherein R₅ is C₁₋₆-alkyl.

Step B:

Reacting a compound of formula (y) wherein Z and T are defined as above and wherein Hlg is chlorine, bromine or iodine and wherein R₅ is C₁₋₆-alkyl, with an appropriate compound of formula U-COOR₅ wherein U is defined as above and R₅ is C₁₋₆-alkyl, through a crosscoupling reaction employing a Pd catalyst such as Pd(PPh₃)₂ or PdCl₂(PPh₃)₂ and a catalytic amount of in example copper(I)iodide and an organic amine base, such as and if needed a cosolvent to give a compound of formula (z)



wherein Z, T, U and R₅ are defined as above.

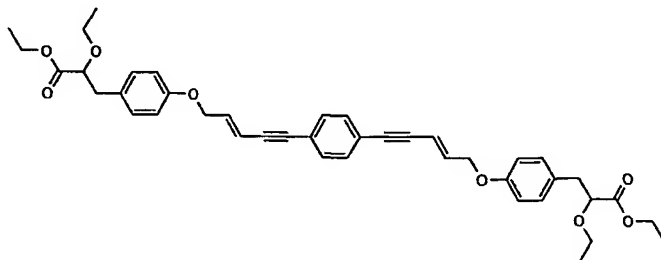
Step C:

Reducing a compound of formula (z), wherein Z, T, U and R₅ are defined as above with a suitable reagent such as diisobutylaluminium hydride or aluminium chloride/lithium aluminium hydride, to give a compound of formula (c).

Using a combination of the above methods, or methods analogous hereof, various compounds may be made within the scope of the present invention.

Example 1 (General procedure A)

(E)(E)(S)(S) 2-Ethoxy-3-{4-[5-(4-[5-(4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynyloxy]-phenyl}-propionic acid ethyl ester



Step A-B:

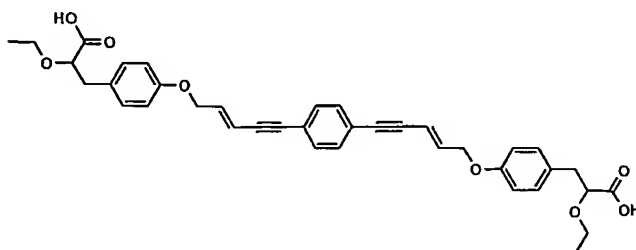
- To a solution of 1,4-diiodobenzene (1.32 g, 4.0 mmol) in diisopropylamine (12 mL) under a nitrogen atmosphere were added copper(I) iodide (60 mg, 0.3 mmol) and tetrakis(triphenylphosphine)palladium (80 mg, 0.07 mmol). After the mixture stirred for 1 h, a solution of 2-penten-4-yn-1-ol (1.0 g, 12.0 mmol) in diisopropylamine (7 mL) was added. After stirring under a nitrogen at 60°C for 8 h, the reaction mixture was filtered and the filtrate evaporated to dryness. The product was purified by flash chromatography using toluene/ethyl acetate (2:1) graduated to ethyl acetate as eluent to give 520 mg (55%) of (E)(E) 5-[4-(5-hydroxy-pent-3-en-1-ynyl)-phenyl]-pent-2-en-4-yn-1-ol.
- ¹H NMR (CDCl₃): δ 1.47 (2H, bs), 4.28 (2H, bs), 5.97 (2H, dt), 6.38 (2H, dt), 7.38 (4H, s).

Step C:

- Under a atmosphere of nitrogen, azodicarboxylic dipiperidide (504 mg, 2.0 mmol) was added at 0-5°C to a stirred solution of tributylphosphine (404 mg, 2.0 mmol), (S)-2-ethoxy-3-(4-hydroxyphenyl)-propionic acid ethyl ester (*Tetrahedron Letters*, Vol. **35**, No 19, 3139-3142, 1994)(357 mg, 1.5 mmol) and (E)(E) 5-[4-(5-hydroxy-pent-3-en-1-ynyl)-phenyl]-pent-2-en-4-yn-1-ol (120 mg, 0.5 mmol) in dry THF (25 mL). After 24 h the reaction mixture was filtered, and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography using toluene/ethyl acetate (19:1) graduated to toluene/ethyl acetate (4:1) as eluent to give 90 mg (27%) of the title compound.
- ¹H NMR (CDCl₃): δ 1.18 (6H, t), 1.23 (6H, t), 2.95 (4H, d), 3.30-3.43 (2H, m), 3.55-3.67 (2H, m), 3.98 (2H, t), 4.18 (4H, q), 4.63 (4H, dd), 6.07 (2H, dt), 6.39 (2H, dt), 6.85 (4H, d), 7.17 (4H, d), 7.27 (4H, s), 7.37 (4H, s).

Example 2 (General procedure E)

- (E)(E)(S)(S) 3-[4-[5-(4-[5-[4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy]-pent-3-en-1-ynyl)-phenyl]-pent-2-en-4-ynyloxy]-phenyl]-2-ethoxy-propionic acid



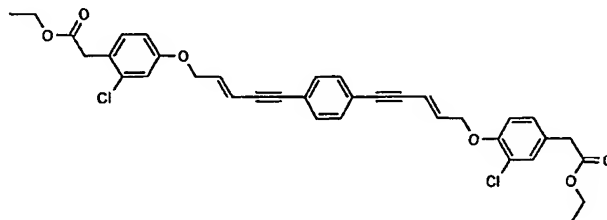
Step A:

To a solution of (*E*)(*E*)(*S*)(*S*) 2-ethoxy-3-{4-[5-(4-{5-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-pent-3-en-1-ynyl}-phenyl)-pent-2-en-4-ynyloxy]-phenyl}-propionic acid ethyl ester (example 1) (88 mg 0.13 mmol) in THF (3 mL) and ethanol (3 mL) was added 1N sodium hydroxide (2 mL). After stirring at room temperature for 1h, the reaction mixture was concentrated in vacuo, added water and 1N hydrochloric acid to pH 1. The product was extracted with dichloromethane (x3) and the combined organic phases were dried (MgSO₄), filtered and concentrated in vacuo to give the title compound as a crystalline product. The product was recrystallised from ethyl acetate and petroleum ether to give 35 mg of the title compound.

¹H NMR (acetone-*d*₆): δ 1.18 (6H, t), 2.95 (2H, dd), 3.10 (2H, dd), 3.42-3.53 (2H, m), 3.55-3.68 (2H, m), 4.07 (2H, dd), 4.63 (3H, dd), 6.07 (2H, dt), 6.39 (2H, dt), 6.85 (4H, d), 7.15 (4H, d), 7.38 (4H, s).

Example 3 (General procedure A)

(*E*)(*E*) 3-Chloro-4-(5-{4-[5-(3-chloro-4-ethoxycarbonylmethyl-phenoxy)-pent-3-en-1-ynyl]-phenyl}-pent-2-en-4-ynyloxy)-phenyl]-acetic acid ethyl ester

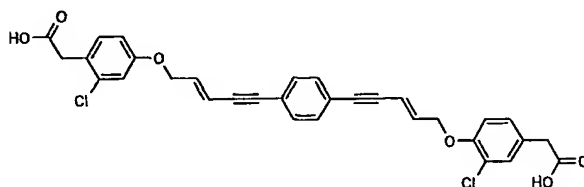
Step C:

Under a atmosphere of nitrogen, azodicarboxylic dipiperidide (504 mg, 2.0 mmol) was added at 0-5°C to a stirred solution of tributylphosphine (404 mg, 2.0 mmol), (3-chloro-4-hydroxyphenyl)propionic acid ethyl ester (322 mg, 1.5 mmol) and (*E*)(*E*) 5-[4-(5-hydroxy-pent-3-en-1-ynyl)-phenyl]-pent-2-en-4-yn-1-ol (example 1, Step A-B) (120 mg, 0.5 mmol) in dry THF (25 mL). After 1 h the reaction mixture was filtered, and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography using toluene graduated to toluene/ ethyl acetate (1:1) as eluent. The product was recrystallised from ethyl acetate to give 150 mg (48%) of the title compound.

¹H NMR (CDCl₃): δ 1.24 (6H, t), 3.53 (4H, s), 4.15 (4H, q), 4.71 (2H, d), 6.15 (2H, dt), 6.40 (2H, dt), 6.88 (2H, d), 7.14 (2H, dd), 7.33 (2H, d), 7.38 (4H, s).

Example 4 (General procedure E)

(*E*)(*E*) [4-(5-{4-[5-(4-Carboxymethyl-3-chloro-phenoxy)-pent-3-en-1-ynyl]-phenyl}-pent-2-en-4-ynyloxy)-3-chloro-phenyl]-acetic acid



5

Step A:

To a solution of (*E*)(*E*) 3-chloro-4-(5-{4-[5-(3-chloro-4-ethoxycarbonylmethyl-phenoxy)-pent-3-en-1-ynyl]-phenyl}-pent-2-en-4-ynyloxy)-phenyl]-acetic acid ethyl ester (example 3) (150 mg 0.24 mmol) in THF (8 mL) and ethanol (4 mL) was added 1N sodium hydroxide (4 mL). After stirring at room temperature for 1h, the reaction mixture was concentrated in vacuo, added water and 1N hydrochloride acid to pH 1. The product was extracted with dichloromethane (x3) and the combined organic phases were dried (MgSO₄), filtered and concentrated in vacuo to give the title compound as a crystalline product. The product was recrystallised from ethyl acetate/THF and petroleum ether to give 90 mg (66%) of the title compound.

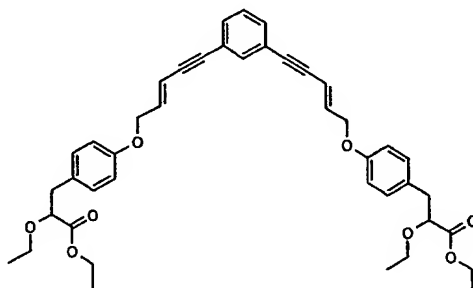
15

¹H NMR (acetone-*d*₆): δ 3.59 (4H, s), 4.82 (4H, d), 6.23 (2H, dt), 6.49 (2H, dt), 7.10 (2H, d), 7.23 (2H, dd), 7.40 (2H, d), 7.47 (4H, s).

Example 5 (General procedure A)

(*E*)(*E*)(*S*)(*S*) 2-Ethoxy-3-{4-[5-(3-{5-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-pent-3-en-1-ynyl}-phenyl)-pent-2-en-4-ynyloxy]-phenyl}-propionic acid ethyl ester

20



Step A-B:

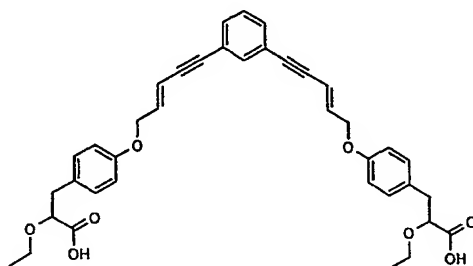
- To a solution of 1,3-diiodobenzene (2.64 g, 8.0 mmol) in diisopropylamine (25 mL) under a nitrogen atmosphere were added copper(I) iodide (75 mg, 0.4 mmol) and tetrakis(triphenylphosphine)palladium (80 mg, 0.07 mmol). After the mixture stirred for 1h, a solution of 2-penten-4-yn-1-ol (2.0 g, 24.0 mmol) in diisopropylamine (10 mL) was added. After stirring at 60°C for 16h, the reaction mixture was filtered and the filtrate evaporated to dryness. The product was purified by flash chromatography using toluene/ ethyl acetate (9:1) graduated to ethyl acetate as eluent to give 1.35 g (71%) of (*E*)(*E*) 5-[3-(5-hydroxy-pent-3-en-1-ynyl)-phenyl]-pent-2-en-4-yn-1-ol.
- ¹H NMR (CDCl₃): δ 4.26 (4H, d), 5.95 (2H, dt), 6.35 (2H, dt), 7.23-7.30 (m, 1H), 7.38 (2H, dd), 7.52 (1H, s).

Step C:

- Under a atmosphere of nitrogen, azodicarboxylic dipiperidide (423 mg, 1.68 mmol) was added at 0-5°C to a stirred solution of tributylphosphine (340 mg, 1.68 mmol), (*S*)-2-ethoxy-3-(4-hydroxyphenyl)-propionic acid ethyl ester (*Tetrahedron Letters*, Vol. 35, No 19, 3139-3142, 1994)(400 mg, 1.68 mmol) and (*E*)(*E*) 5-[3-(5-hydroxy-pent-3-en-1-ynyl)-phenyl]-pent-2-en-4-yn-1-ol (200 mg, 0.84 mmol) in dry THF (20 mL). After 1h the reaction mixture was filtered, and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography using toluene/ ethyl acetate (9:1) as eluent to give 130 mg (23%) of the title compound.
- ¹H NMR (CDCl₃): δ 1.17 (6H, t), 1.22 (6H, t), 2.95 (4H, d), 3.30-3.42 (2H, m), 3.55-3.65 (2H, m), 3.98 (2H, t), 4.18 (4H, q), 4.62 (4H, dd), 6.05 (2H, dt), 6.39 (2H, dt), 6.85 (4H, d), 7.17 (4H, d), 7.23-7.30 (m, 1H), 7.37 (2H, dd), 7.50 (1H, s).

Example 6 (General procedure E)

- (*E*)(*E*)(*S*)(*S*) 3-{4-[5-{3-[5-[4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy]-pent-3-en-1-ynyl]-phenyl}-pent-2-en-4-ynyloxy]-phenyl}-2-ethoxy-propionic acid



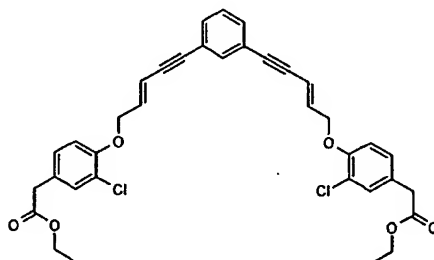
Step A:

To a solution of (*E*)(*E*)(*S*)(*S*) 2-ethoxy-3-{4-[5-(3-{5-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-pent-3-en-1-ynyl]-phenyl)-pent-2-en-4-ynyloxy]-phenyl}-propionic acid ethyl ester (example 5) (130 mg 0.2 mmol) in THF (3 mL) and ethanol (3 mL) was added 1N sodium hydroxide (1.5 mL). After stirring at room temperature for 2h, the reaction mixture was concentrated in vacuo, added water and 1N hydrochloride acid to pH 1. The product was extracted with dichloromethane (x3) and the combined organic phases were dried (MgSO₄), filtered and concentrated in vacuo to give the title compound as a crystalline product. The product was recrystallised from tetrachloromethane and petroleum ether to give 72 mg (58%) of the title compound.

¹H NMR (acetone-*d*₆): δ 1.12 (6H, t), 2.88 (2H, dd), 3.02 (2H, dd), 3.32-3.43 (2H, m), 3.57-3.68 (2H, m), 4.04 (2H, dd), 4.70 (4H, dd), 6.15 (2H, dt), 6.47 (2H, dt), 6.90 (4H, d), 7.23 (4H, d), 7.38-7.49 (m, 1H), 7.37 (2H, dd), 7.52 (1H, s).

Example 7 (General procedure A)

(*E*)(*E*) [3-Chloro-4-(5-{3-[5-(2-chloro-4-ethoxycarbonylmethyl-phenoxy)-pent-3-en-1-ynyl]-phenyl}-pent-2-en-4-ynyloxy)-phenyl]-acetic acid ethyl ester

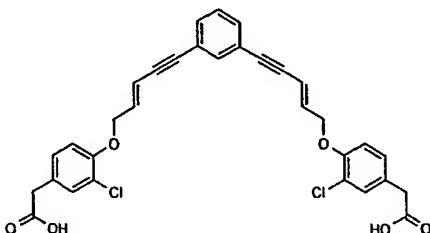
Step C:

Under a atmosphere of nitrogen, azodicarboxylic dipiperidide (423 mg, 1.68 mmol) was added at 0-5°C to a stirred solution of tributylphosphine (340 mg, 1.68 mmol), (3-chloro-4-hydroxyphenyl)propionic acid ethyl ester (361 mg, 1.68 mmol) and (*E*)(*E*) 5-[3-(5-hydroxy-pent-3-en-1-ynyl)-phenyl]-pent-2-en-4-yn-1-ol (example 5, Step A-B) (200 mg, 0.84 mmol) in dry THF (20 mL). After 1 h the reaction mixture was filtered, and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography using toluene/ ethyl acetate (19:1) as eluent to give 180 mg (34%) of the title compound.

¹H NMR (CDCl₃): δ 1.26 (6H, t), 3.53 (4H, s), 4.15 (4H, q), 4.69 (2H, d), 6.13 (2H, dt), 6.39 (2H, dt), 6.87 (2H, d), 7.12 (2H, dd), 7.20-7.38 (5H, m), 7.50 (1H, s).

Example 8 (General procedure E)

(*E*)(*E*) [4-(5-{3-[5-(4-Carboxymethyl-2-chloro-phenoxy)-pent-3-en-1-ynyl]-phenyl}-pent-2-en-4-ynyloxy)-3-chloro-phenyl]-acetic acid



5

Step A:

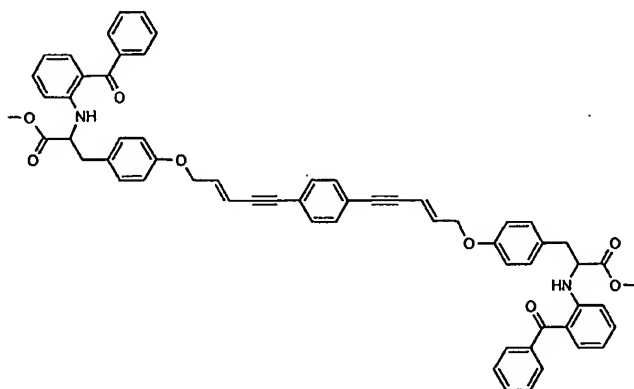
To a solution of (*E*)(*E*) [3-chloro-4-(5-{3-[5-(2-chloro-4-ethoxycarbonylmethyl-phenoxy)-pent-3-en-1-ynyl]-phenyl}-pent-2-en-4-ynyloxy)-phenyl]-acetic acid ethyl ester (ex-
 10 ample 7) (180 mg 0.28 mmol) in THF (3 mL) and ethanol (3 mL) was added 1N sodium hydroxide (1.5 mL).

After stirring at room temperature for 4h, the reaction mixture was concentrated in vacuo, added water and 1N hydrochloride acid to pH 1. The product was extracted with dichloro-
 15 methane/isopropanol (x3) and the combined organic phases were dried (MgSO₄), filtered and concentrated in vacuo to give 125 mg of the title compound as a crystalline product.

¹H NMR (acetone-*d*₆): δ 3.60 (4H, s), 4.82 (4H, d), 6.23 (2H, dt), 6.50 (2H, dt), 7.10 (2H, d), 7.23 (2H, dd), 7.39-7.50 (5H, m), 7.53 (1H, s).

Example 9 (General procedure A)

(*E*)(*E*)(*S*)(*S*) 2-(2-Benzoyl-phenylamino)-3-(4-{5-[4-(5-{4-[2-(2-benzoyl-phenylamino)-2-methoxycarbonyl-ethyl]-phenoxy}-pent-3-en-1-ynyl)-phenyl]-pent-2-en-4-ynyloxy}-phenyl)-propionic acid methyl ester



5

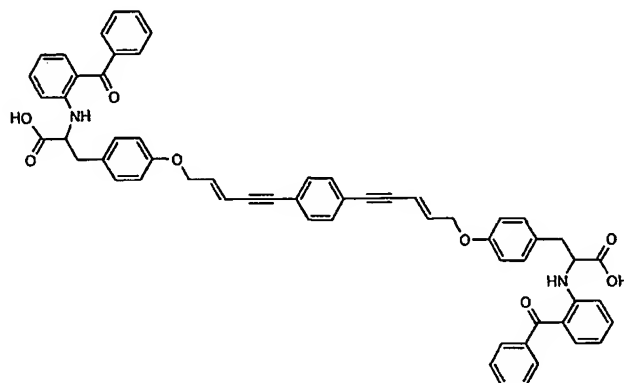
Step C:

Under a atmosphere of nitrogen, azodicarboxylic dipiperidide (1.0 g, 4.0 mmol) was added at 0-5°C to a stirred solution of tributylphosphine (808 mg, 4.0 mmol), (*S*)-2-(2-benzoyloxy-phenylamino)-3-(4-hydroxyphenyl)-propionic acid methyl ester (820 mg, 2.18 mmol) and (*E*)(*E*) 5-[4-(5-hydroxy-pent-3-en-1-ynyl)-phenyl]-pent-2-en-4-yn-1-ol (example 1, Step A-B) (260 mg, 1.1 mmol) in dry THF (20 mL). After 2 h the reaction mixture was filtered, and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography using toluene/ ethyl acetate (19:1) as eluent, to give 370 mg (36%) of the title compound as an oil.

15 ¹H NMR (CDCl₃): δ 3.12 (2H, dd), 3.23 (2H, dd), 3.70 (6H, s), 4.39 (2H, q), 4.60 (4H, d), 6.04 (2H, dt), 6.37 (2H, dt), 6.53-6.67 (4H, m), 6.85 (4H, d), 7.14-7.63 (22H, m), 8.87 (2H, d).

Example 10 (General procedure E)

(*E*)(*E*)(*S*)(*S*) 2-(2-Benzoyl-phenylamino)-3-(4-{5-[4-(5-{4-[2-(2-benzoyl-phenylamino)-2-carboxy-ethyl]-phenoxy}-pent-3-en-1-ynyl)-phenyl]-pent-2-en-4-ynyloxy}-phenyl)-propionic acid



5

Step A:

To a solution of (*E*)(*E*)(*S*)(*S*) 2-(2-benzoyl-phenylamino)-3-(4-{5-[4-(5-{4-[2-(2-benzoyl-phenylamino)-2-methoxycarbonyl-ethyl]-phenoxy}-pent-3-en-1-ynyl)-phenyl]-pent-2-en-4-ynyloxy}-phenyl)-propionic acid methyl ester (example 9) (370 mg 0.39 mmol) in THF (3 mL) and ethanol (3 mL) was added 1N sodium hydroxide (2 mL). After stirring at room temperature for 1h, the reaction mixture was concentrated in vacuo, added water and 1N hydrochloride acid to pH 1. The product was extracted with dichloromethane (x3) and the combined organic phases were dried (MgSO₄), filtered and concentrated in vacuo to give the title compound as a crystalline product. The product was recrystallised from ethyl acetate and petroleum ether to give 200 mg of the title compound.

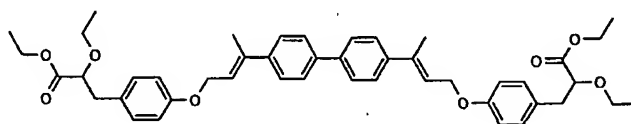
15

¹H NMR (CDCl₃): δ 3.15 (2H, dd), 3.29 (2H, dd), 4.40 (2H, bs), 4.55 (4H, d), 6.03 (2H, d), 6.35 (2H, dt), 6.57-6.74 (4H, m), 6.82 (4H, d), 7.22 (4H, d), 7.30-7.63 (18H, m), 8.85 (2H, bs).

Example 11 (General procedure F)

(*E*)(*E*)(*S*)(*S*) 2-Ethoxy-3-[4-[3-(4'-{3-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-1-methyl-propenyl]-biphenyl-4-yl)-but-2-enyloxy]-phenyl]-propionic acid ethyl ester

20



Step A:

Sodium (5.52 g, 0.24 mol) was dissolved in ethanol (200 mL). A solution of triethylphosphonoacetate (62.7 g, 0.28 mol) in ethanol (100 mL) was slowly added. The mixture was stirred for 20 min. and added a solution of 4-iodoacetophenone (49.21 g, 0.20 mol) in hot ethanol (200 mL). The mixture was stirred at 80°C for 66h. The mixture was cooled and ethanol evaporated. The residue was added 1N HCl (400 mL) and ethyl acetate (400 mL). The aqueous layer was further extracted with ethyl acetate (2 x 200 mL). The combined organic phases were washed with brine, dried (MgSO₄), filtered and evaporated. The product was purified by column chromatography using heptane/ethyl ether (39:1) as eluent to give 30.0 g (46%) of (*E*) 3-(4-iodophenyl)but-2-enoic acid ethyl ester.

¹H NMR (CDCl₃): δ 1.31 (3H, t), 2.53 (3H, s), 4.21 (2H, q), 6.11 (1H, s), 7.19 (2H, d), 7.69 (2H, d).

Step B:

Under a atmosphere of nitrogen, (*E*) 3-(4-iodophenyl)but-2-enoic acid ethyl ester (10.1 g, 32.0 mmol) was dissolved in dry THF (300 mL). The solution was cooled to -15°C and slowly added a 1M solution of DIBAL-H in toluene (96.0 ml, 96.0 mmol). The mixture was slowly warmed to room temperature and stirred for 1h. Methanol (50 ml) was carefully added, followed by 1N HCl (500 ml) and the resulting mixture extracted with ethyl acetate (3 x 500ml). The combined organic extracts were washed with brine, dried (MgSO₄), and evaporated to give 8.8 g of (*E*) 3-(4-iodophenyl)but-2-en-1-ol.

¹H NMR (CDCl₃): δ 1.42 (1H, ds), 2.04 (3H, s), 4.35 (2H, d), 5.97 (1H, t), 7.13 (2H, d), 7.63 (2H, d).

Step C:

Tetrakis(triphenylphosphine)palladium(0) (0.46 g, 0.4 mmol, 4 mol%) was added, under nitrogen, to a stirred solution of (*E*) 3-(4-iodophenyl)but-2-en-1-ol (2.74 g, 10.0 mmol) in DME (100 mL), and the solution stirred at room temperature for 10 min. Aqueous 2M sodium carbonate (30.0 ml, 60.0 mmol) was then added, the mixture stirred for 10 min, then 4-acetylboronic acid (3.28 g, 20.0 mmol) was added, and the reaction mixture heated to 65°C for 18 h, under reflux. and at room temperature for another 3 days. The reaction mixture was diluted with 1N HCl (200 ml) and the products extracted into ethyl acetate (2 x 200 ml). The combined organic extracts were washed with brine, dried (MgSO₄), and evaporated to give the crude product, which was purified by column chromatography on silica gel using heptane/ethyl acetate (3:2) eluent) graduated to heptane/ethyl acetate (2:3) as eluent, to give 2.0 g (75%) of (*E*) 1-[4'-(3-hydroxy-1-methyl-propenyl)-biphenyl-4-yl]-ethanone.

¹H NMR (CDCl₃) δ: 2.12 (3H, s), 2.64 (3H, s), 4.41 (2H, q), 6.07 (1H, t), 7.51 (2H, d), 7.61 (2H, d), 7.71 (2H, d), 8.03 (2H, d).

Step D:

To a suspension of (*E*) 1-[4'-(3-hydroxy-1-methyl-propenyl)-biphenyl-4-yl]-ethanone (1.1 g, 4.13 mmol) in dichloromethane (40 mL) was under a atmosphere of nitrogen added imidazole (0.42 g, 6.20 mmol) and *tert*-butyldimethylsilyl chloride (0.78 g, 5.15 mmol). The mixture was stirred at room temperature for 18 h. Dichloromethane (15 mL) was added and the reaction mixture was washed with water, sodium hydrogencarbonate solution and brine. The organic phase was dried (MgSO₄), filtered and concentrated in vacuo. The residue was submitted to column chromatography on silica gel, using heptane/ethyl acetate (4:1) as eluent, to give 1.36 g (87%) of (*E*) 1-[4'-[3-(*tert*-butyldimethylsilanyloxy)-1-methylpropenyl]-biphenyl-4-yl]ethanone. M.p. 100-106°C.

¹H NMR (CDCl₃) δ: 0.13 (6H, s), 0.97 (9H, s), 2.10 (3H, s), 2.65 (3H, s), 4.13 (2H, d), 5.98 (1H, dt), 7.51 (2H, d), 7.60 (2H, d), 7.69 (2H, d), 8.02 (2H, d).

Step E:

Sodium (0.42 g, 18.0 mmol) was added to ethanol (50 mL) at 20°C and the mixture stirred until the metal had fully reacted. Triethyl phosphonoacetate (2.4 mL, 12.0 mmol) was added, the mixture stirred for 5 min., then (*E*) 1-[4'-[3-(*tert*-butyldimethylsilanyloxy)-1-methylpropenyl]-biphenyl-4-yl]ethanone (1.14 g, 3.0 mmol) was added to the stirred solution. The mixture was stirred at room temperature for 24h. The reaction mixture was added water and the product extracted with ethyl acetate (2x). The combined organic phases were washed with brine, dried (MgSO₄), filtered and concentrated in vacuo. The residue was submitted to column chromatography on silica gel, using heptane/ethyl acetate (4:1) as eluent, to give 1.13 g (81%) of (*E*)(*E*) 3-(4'-[3-[(*tert*-butyldimethylsilyl)-methoxy]-1-methylpropenyl]-biphenyl-4-yl)-but-2-enoic acid ethyl ester.

¹H NMR (CDCl₃) δ: 0.12 (6H, s), 0.92 (9H, s), 1.32 (3H, t), 2.08 (3H, s), 2.62 (3H, s), 4.22 (2H, q), 4.42 (2H, d), 5.97 (1H, dt), 6.20 (1H, d), 7.43-7.63 (8H, m).

Step F:

A 1M solution of DIBAL-H in toluene (7.3 mL, 7.3 mmol) was, under a atmosphere of nitrogen, added dropwise at -70°C over 20 min. to a stirred solution of (*E*)(*E*) 3-(4'-[3-[(*tert*-butyldimethylsilyl)-methoxy]-1-methylpropenyl]-biphenyl-4-yl)-but-2-enoic acid ethyl ester (1.13 g, 2.43 mmol) in dry THF (25 mL). The mixture was stirred for 30 min. followed by 2h at room temperature. Ethanol (1 mL) was carefully added, followed by 1N HCl (50 mL) and the resulting mixture extracted with ethyl acetate (2 x 50 mL). The combined organic extracts

were washed with brine, dried (MgSO_4), and evaporated to give 1.02 g (99%) of *(E)(E)* 3-(4'-{3-[(*tert*-butyldimethylsilyl)-methoxy]-1-methylpropenyl}-biphenyl-4-yl)-but-2-en-1-ol.

^1H NMR (CDCl_3) δ : 0.13 (6H, s), 0.96 (9H, s), 1.57 (1H, s), 2.07 (3H, s), 2.13 (3H, s), 4.37-4.46 (4H, m), 5.85 (1H, t), 5.93 (1H, t), 7.46-7.52 (4H, m), 7.53-7.61 (4H, m).

5 Step G:

Under a atmosphere of nitrogen, azodicarboxylic dipiperidide (0.91 g, 3.62 mmol) was added at 0-5°C to a stirred solution of tributylphosphine (0.89 mL, 3.62 mmol), (*S*)-ethyl 2-ethoxy-3-(4-hydroxyphenyl)-propionate (0.60 g, 2.53 mmol) and *(E)(E)* 3-(4'-{3-[(*tert*-butyldimethylsilyl)-methoxy]-1-methylpropenyl}-biphenyl-4-yl)-but-2-en-1-ol (1.02 g, 2.41 mmol) in dry THF (15 ml). The mixture was warmed to room temperature, and stirred for 18 h. The resulting mixture was diluted with water and ethyl acetate, the aqueous layer collected and further extracted with ethyl acetate. The organic layers were combined, washed with brine, dried (MgSO_4) and evaporated. The crude product was then purified by column chromatography on silica using heptane/ethyl acetate (4:1) as eluent to give 1.18 g (76%) of *(E)(E)(S)* 3-{4-[3-(4'-{3-[(*tert*-butyldimethylsilyl)-methoxy]-1-methylpropenyl}-biphenyl-4-yl)-but-2-enyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester.

^1H NMR (CDCl_3) δ : 0.13 (6H, s), 0.93 (9H, s), 1.18 (3H, t), 1.23 (3H, t), 2.07 (3H, s), 2.18 (3H, s), 2.95 (2H, d), 3.31-3.42 (1H, m), 3.55-3.67 (1H, m), 3.98 (1H, t), 4.17 (2H, q), 4.42 (2H, d), 4.73 (2H, d), 5.95 (1H, t), 6.12 (1H, t), 6.88 (2H, d), 7.18 (2H, d), 7.45-7.60 (8H, m).

20 Step H:

A solution of *(E)(E)(S)* 3-{4-[3-(4'-{3-[(*tert*-butyldimethylsilyl)-methoxy]-1-methylpropenyl}-biphenyl-4-yl)-but-2-enyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester (1.18 g, 1.84 mmol) in dry THF was cooled on ice and slowly added a 1.1 M solution of tetrabutylammonium fluoride in THF (1.93 mL, 1.93 mmol). The reaction mixture was stirred at room temperature for 3h. The mixture was diluted with water and ethyl acetate, the aqueous layer collected and further extracted with ethyl acetate. The organic layers were combined, washed with brine, dried (MgSO_4) and evaporated to give 0.94 g of *(E)(E)(S)* 2-ethoxy-3-(4-{3-[4'-{3-hydroxy-1-methyl-propenyl}-biphenyl-4-yl]-but-2-enyloxy}-phenyl)-propionic acid ethyl ester.

30 ^1H NMR (CDCl_3) δ : 1.18 (3H, t), 1.22 (3H, t), 2.12 (3H, s), 2.18 (3H, s), 2.96 (2H, d), 3.30-3.42 (1H, m), 3.53-3.67 (1H, m), 3.98 (1H, t), 4.17 (2H, q), 4.40 (2H, d), 4.74 (2H, d), 6.04 (1H, t), 6.12 (1H, t), 6.88 (2H, d), 7.18 (2H, d), 7.45-7.62 (8H, m).

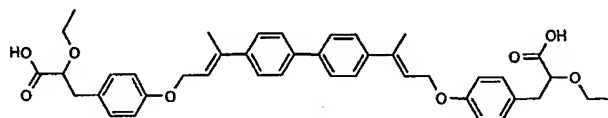
Step I:

Under a atmosphere of nitrogen, azodicarboxylic dipiperidide (0.50 g, 1.89 mmol) was added at 0-5°C to a stirred solution of tributylphosphine (0.37 mL, 1.89 mmol), (S)-ethyl 2-ethoxy-3-(4-hydroxyphenyl)-propionate (0.32 g, 1.32 mmol) and (E)(E)(S) 2-ethoxy-3-(4-{3-[4'-{3-hydroxy-1-methyl-propenyl)-biphenyl-4-yl]-but-2-enyloxy}-phenyl)-propionic acid ethyl ester (0.65 g, 1.26 mmol) in dry THF (15 ml). The mixture was warmed to room temperature, and stirred for 18 h. The resulting mixture was diluted with water and ethyl acetate, the aqueous layer collected and further extracted with ethyl acetate. The organic layers were combined, washed with brine, dried (MgSO₄) and evaporated to give 580 mg (63%) of the title compound.

¹H NMR (CDCl₃) δ: 1.17 (6H, t), 1.22 (6H, t), 2.16 (6H, s), 2.97 (4H, d), 3.27-3.43 (2H, m), 3.52-3.69 (2H, m), 3.98 (2H, t), 4.17 (4H, q), 4.73 (4H, d), 6.12 (2H, t), 6.88 (4H, d), 7.18 (4H, d), 7.43-7.63 (8H, m).

Example 12 (General procedure E)

(E)(E)(S)(S) 3-{4-[3-(4'-{3-[4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy]-1-methyl-propenyl}-biphenyl-4-yl)-but-2-enyloxy]-phenyl}-2-ethoxy-propionic acid

Step A:

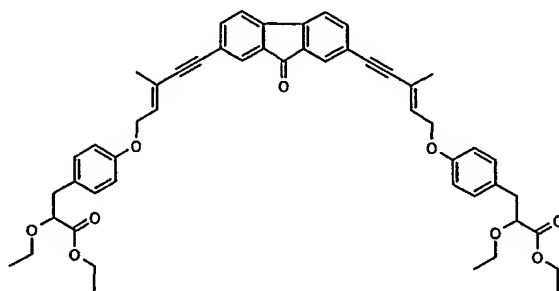
To a solution of (E)(E)(S)(S) 2-ethoxy-3-{4-[3-(4'-{3-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-1-methyl-propenyl}-biphenyl-4-yl)-but-2-enyloxy]-phenyl}-propionic acid ethyl ester (example 11) (367 mg 0.5 mmol) in ethanol (10 mL) was added 1N sodium hydroxide (2 mL). The reaction mixture was stirred at room temperature for 18h, and at 60°C 1h. The resulting mixture was diluted with water and ethyl acetate, the aqueous layer collected and further extracted with ethyl acetate (3x). The organic layers were combined, washed with brine, dried (MgSO₄) and evaporated to give 180 mg (53%) of the title compound.

¹H NMR (CDCl₃ + 1 dr. DMSO): δ 1.15 (6H, t), 2.93 (2H, dd), 3.04 (2H, dd), 3.30-3.42 (2H, m), 3.60-3.71 (2H, m), 3.95 (2H, dd), 4.73 (4H, d), 6.11 (2H, t), 6.88 (4H, d), 7.21 (4H, d), 7.51 (4H, d), 7.57 (4H, d).

Example 13 (General procedure A)

(*E*)(*E*)(*S*)(*S*) 2-Ethoxy-3-{4-[5-(7-{5-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-3-methyl-pent-3-en-1-ynyl]-9-oxo-9*H*-fluoren-2-yl)-3-methyl-pent-2-en-4-ynyloxy]-phenyl}-propionic acid ethyl ester

5

Step A-B:

To a solution of 2,7-dibromo-9-fluorenone (338 mg, 1.0 mmol) in dry THF (17 mL) under a nitrogen atmosphere were added copper(I) iodide (30 mg, 0.16 mmol) and di-chlorobis(triphenylphosphine)palladium (II) (70 mg, 0.10 mmol), *trans*-3-methyl-2-penten-4-yn-1-ol (481 mg, 5.0 mmol) and dry isopropylamine (17 mL). After stirring at room temperature for 6h, the reaction mixture was filtered and the filtrate evaporated to dryness. The product was purified by column chromatography on silica using dichloromethane/ THF (10:1) as eluent to give 200 mg (71%) of (*E*)(*E*) 2,7-bis-(5-hydroxy-3-methyl-pent-3-en-1-ynyl)-fluorene-9-one.

¹H NMR (DMSO): δ 1.87 (6H, s), 4.10 (4H, t), 4.83 (2H, t), 6.05 (2H, dt), 7.57 (2H, s), 7.66 (2H, d), 7.82 (2H, d).

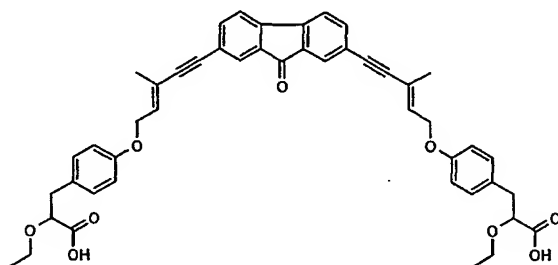
Step C:

To a solution of (*E*)(*E*) 2,7-bis-(5-hydroxy-3-methyl-pent-3-en-1-ynyl)-fluorene-9-one (179 mg, 0.49 mmol) in dry THF (10 mL) was under a atmosphere of nitrogen added triphenylphosphine (385 mg, 1.47 mmol) and (*S*)-2-ethoxy-3-(4-hydroxyphenyl)-propionic acid ethyl ester (467 mg, 1.96 mmol) and the mixture was cooled on ice. After stirring for 10 min. diethylazodicarboxylate (227 mg, 0.256 mmol) was added. After stirring for 1h the reaction mixture was added water and dichloromethane. The aqueous layer was further extracted with dichloromethane (2 x). The combined organic phases were dried (MgSO₄), filtered and evaporated. The product was purified by column chromatography using dichloromethane/THF (10:1) as eluent to give 220 mg (55%) of the title compound.

¹H NMR (CDCl₃): δ 1.17 (6H, t), 1.22 (6H, t), 1.98 (6H, s), 2.95 (4H, d), 3.30-3.40 (2H, m), 3.54-3.65 (2H, m), 3.98 (2H, t), 4.18 (4H, q), 4.62 (4H, d), 6.20 (2H, t), 6.85 (4H, d), 7.17 (4H, d), 7.43 (2H, d), 7.52 (2H, d), 7.68 (2H, s).

Example 14 (General procedure E)

- 5 (E)(E)(S)(S) 3-{4-[5-(7-{5-[4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy]-3-methyl-pent-3-en-1-ynyl]-9-oxo-9H-fluoren-2-yl)-3-methyl-pent-2-en-4-ynyloxy]-phenyl}-2-ethoxy-propionic acid



Step A:

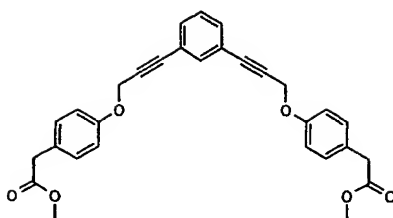
- 10 To a solution of (E)(E)(S)(S) 2-ethoxy-3-{4-[5-(7-{5-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-3-methyl-pent-3-en-1-ynyl]-9-oxo-9H-fluoren-2-yl)-3-methyl-pent-2-en-4-ynyloxy]-phenyl}-propionic acid ethyl ester (example 13) (185 mg, 0.23 mmol) in ethanol (10 mL) was added 1N sodium hydroxide (2.3 mL). After stirring at 60°C for 30 min., the reaction mixture was concentrated in vacuo, added water and 1N hydrochloride acid to pH 1. The product was extracted with dichloromethane (x3) and the combined organic phases were dried (MgSO₄), filtered and concentrated in vacuo to give 160 mg of the title compound as a crystalline product.

- 15 ¹H NMR (CDCl₃): δ 1.18 (6H, t), 1.98 (6H, s), 2.97 (2H, dd), 3.10 (2H, dd), 3.38-3.51 (2H, m), 3.57-3.69 (2H, m), 4.05 (2H, dd), 4.63 (4H, d), 6.17 (2H, t), 6.85 (4H, d), 7.15 (4H, d), 7.41 (2H, d), 7.52 (2H, d), 7.65 (2H, s).

Example 15 (General procedure A)

[4-(3-{3-[3-(4-Methoxycarbonylmethyl-phenoxy)-prop-1-ynyl]-phenyl}-prop-2-ynyloxy)-phenyl]-acetic acid methyl ester

62

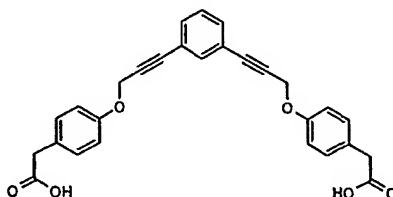
**Step C:**

Under a atmosphere of nitrogen, azodicarboxylic dipiperidide (406 mg, 1.61 mmol) was added at 0-5°C to a stirred solution of tributylphosphine (325 mg, 1.61 mmol), methyl 4-hydroxyphenylacetate (268 mg, 1.61 mmol) and 3-[3-(3-hydroxy-prop-1-ynyl)-phenyl]-prop-2-yn-1-ol (*J Pharmacol Exp Ther* 298: 1260-1268, 2001) (150 mg, 0.81 mmol) in dry THF (20 mL). The reaction mixture was stirred for 1 h at 0-5°C, and at room temperature for 16 h. The reaction mixture was concentrated in vacuo. The crude product was purified by flash chromatography using heptane/ ethyl acetate (1:1) as eluent to give 218 mg (56%) of the title compound.

¹H NMR (DMSO): δ 3.35 (6H, s), 3.53 (4H, s), 5.03 (4H, s), 6.93 (2H, d), 7.22 (2H, d), 7.40 (2H, dd), 7.45-7.50 (3H, m).

Example 16 (General procedure E)

[4-(3-{3-[3-(4-Methoxycarbonylmethyl-phenoxy)-prop-1-ynyl]-phenyl}-prop-2-ynyloxy)-phenyl]-acetic acid

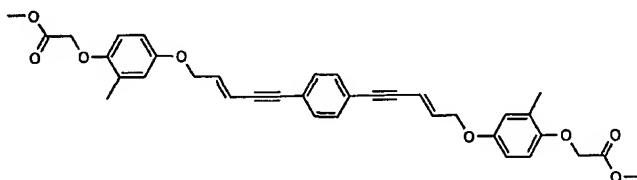
**Step A:**

To a solution of [4-(3-{3-[3-(4-methoxycarbonylmethyl-phenoxy)-prop-1-ynyl]-phenyl}-prop-2-ynyloxy)-phenyl]-acetic acid methyl ester (example 15) (200 mg, 0.42 mmol) in ethanol (3 mL) was added 1N sodium hydroxide (1.6 mmol, 1.6 mL). After stirring at room temperature for 16 h, the reaction mixture was added 1N hydrochloride acid to pH 1. The product was isolated by filtration and dried to give 100 mg (53%) of the title compound as a crystalline product.

¹H NMR (acetone-*d*₆): δ 3.55 (4H, s), 5.00 (4H, s), 7.00 (4H, d), 7.27 (4H, d), 7.38 (1H, dd), 7.43 (1H, s), 7.48 (2H, dd).

Example 17 (General procedure A)

(*E*)(*E*) [4-(5-[4-[5-(4-Methoxycarbonylmethoxy-3-methyl-phenoxy)-pent-3-en-1-ynyl]-phenyl]-pent-2-en-4-ynyloxy)-2-methyl-phenoxy]-acetic acid methyl ester



5

Step C:

Under a atmosphere of nitrogen, azodicarboxylic dipiperidide (252 mg, 1.0 mmol) was added at room emperature to a stirred solution of tributylphosphine (202 mg, 1.0 mmol), (4-hydroxy-2-methyl-phenoxy)-acetic acid methyl ester (WO 01/00603 A1)(170 mg, 0.86 mmol) and (*E*)(*E*) 5-[4-(5-hydroxy-pent-3-en-1-ynyl)-phenyl]-pent-2-en-4-yn-1-ol (example 1, Step A-B) (103 mg, 0.43 mmol) in dry THF (20 mL). After 2 h the reaction mixture was added water and the product extracted with ethyl acetate. The combined organic phases were dried, filtered and concentrated in vacuo. The crude product was purified by flash chromatography using heptane graduated to heptane/ ethyl acetate (1:1) as eluent to give 10 mg of the title compound.

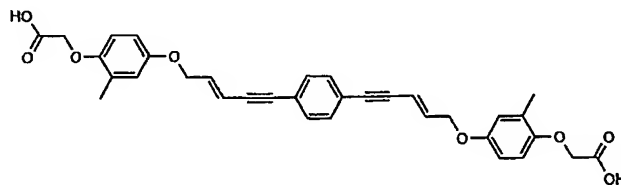
15

¹H NMR (CDCl₃): δ 2.28 (6H, s), 3.78 (6H, s), 4.54-4.60 (4H, m), 4.60 (4H, s), 6.03 (2H, dt), 6.38 (2H, dt), 6.66 (4H, s), 6.78 (2H, s), 7.37 (4H, s).

Example 18 (General procedure E)

(*E*)(*E*) [4-(5-[4-[5-(4-Methoxycarbonylmethoxy-3-methyl-phenoxy)-pent-3-en-1-ynyl]-phenyl]-pent-2-en-4-ynyloxy)-2-methyl-phenoxy]-acetic acid

20

**Step A:**

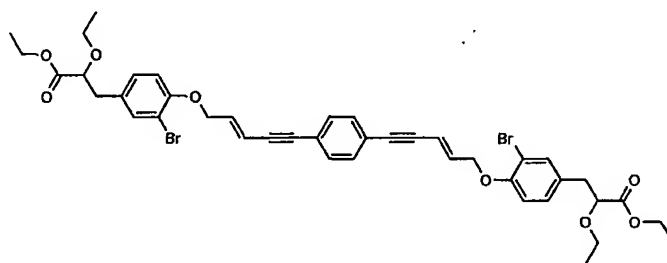
To a solution of (*E*)(*E*) [4-(5-[4-[5-(4-methoxycarbonylmethoxy-3-methyl-phenoxy)-pent-3-en-1-ynyl]-phenyl]-pent-2-en-4-ynyloxy)-2-methyl-phenoxy]-acetic acid methyl ester (example 17) (15 mg, 0.025 mmol) in ethanol (15 mL) and THF (5 mL) was added 1N sodium

25

hydroxide (1.0 mL). After stirring at room temperature for 30 min., the reaction mixture was added water and 1N hydrochloride acid to pH 1. The product was extracted with dichloromethane (x3) and the combined organic phases were dried (MgSO_4), filtered and concentrated in vacuo to give 10 mg of the title compound.

5 **Example 19** (General procedure A)

(E)(E)(S)(S) 3-{3-Bromo-4-[5-(4-{5-[2-bromo-4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-pent-3-en-1-ynyl]-phenyl)-pent-2-en-4-ynyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester



10 **Step C:**

a) To a stirred solution of (S)-2-ethoxy-3-(4-hydroxyphenyl)-propionic acid ethyl ester (*Tetrahedron Letters*, Vol. 35, No 19, 3139-3142, 1994) (9.5 g, 40 mmol) in dry methylene chloride (100 ml) was over 1 h dropwise added a solution of bromine in methylene chloride (40 ml) at room temperature. The reaction was stirred for 60 min, washed with saturated sodium sulfite and brine. The organic phase was dried (MgSO_4) and evaporated. The residue was purified by column chromatography using heptane:ethyl acetate (9:1) as eluent to give 11.25 g (88 %) of (S)-3-(3-bromo-4-hydroxy-phenyl)-2-ethoxy-propionic acid ethyl ester.

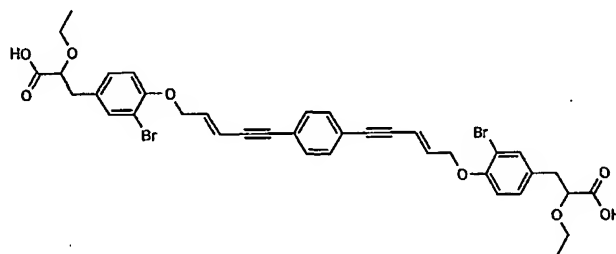
^1H NMR (CDCl_3): δ 1.18 (3H, t), 1.23 (3H, t), 2.92 (2H, d), 3.30-3.43 (1H, m), 3.57-3.70 (1H, m), 3.96 (1H, dd), 4.18 (4H, q), 5.72 (1H, s), 6.90 (1H, d), 7.09 (1H, dd), 7.35 (1H, d).

b) Under a atmosphere of nitrogen, azodicarboxylic dipiperidide (504 mg, 2.0 mmol) was added to a stirred solution of tributylphosphine (325 mg, 1.3 mmol), (S)-3-(3-bromo-4-hydroxy-phenyl)-2-ethoxy-propionic acid ethyl ester (450 mg, 1.89 mmol) and (E)(E) 5-[4-(5-hydroxy-pent-3-en-1-ynyl)-phenyl]-pent-2-en-4-yn-1-ol (example 1, step A-B) (150 mg, 0.63 mmol) in dry THF (30 mL). After 1 h the reaction mixture was added water and the product extracted with ethyl acetate (3x). The combined organic phases were dried, filtered and concentrated in vacuo. The crude product was purified by flash chromatography using heptane/ethyl acetate (4:1) as eluent to give 250 mg of the title compound.

¹H NMR (CDCl₃): δ 1.18 (6H, t), 1.23 (6H, t), 2.95 (4H, m), 3.30-3.43 (2H, m), 3.55-3.67 (2H, m), 3.98 (2H, t), 4.18 (4H, q), 4.63 (4H, dd), 6.07 (2H, dt), 6.39 (2H, dt), 6.80 (2H, d), 7.13 (2H, dd), 7.38 (4H, s), 7.45 (2H, dd).

Example 20 (General procedure E)

(E)(E)(S)(S) 3-{3-Bromo-4-[5-(4-[5-[2-bromo-4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-pent-3-en-1-ynyl]-phenyl)-pent-2-en-4-ynyloxy]-phenyl}-2-ethoxy-propionic acid



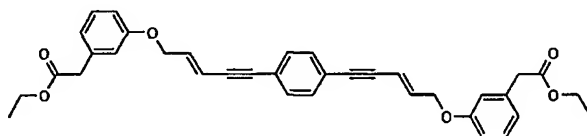
Step A:

To a solution of (E)(E)(S)(S) 3-{3-bromo-4-[5-(4-[5-[2-bromo-4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-pent-3-en-1-ynyl]-phenyl)-pent-2-en-4-ynyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester (example 19) (250 mg 0.30 mmol) in THF (2 mL) and ethanol (3 mL) was added 1N sodium hydroxide (3 mL). After stirring at room temperature for 1h, the reaction mixture was concentrated in vacuo, added water and 1N hydrochloric acid to pH 1. The product was extracted with ethyl acetate (x3) and the combined organic phases were washed with water, dried (MgSO₄), filtered and concentrated in vacuo to give 230 mg of the title compound.

^1H NMR (CDCl_3): δ 1.18 (6H, t), 2.93 (2H, dd), 3.04 (2H, dd), 3.35-3.48 (2H, m), 3.58-3.72 (2H, m), 4.03 (2H, dd), 4.68 (4H, dd), 6.18 (2H, dt), 6.39 (2H, dt), 6.80 (2H, d), 7.15 (2H, dd), 7.39 (4H, s), 7.49 (2H, d), 10.24 (2H, bs).

Example 21 (General procedure A)

- 5 (E)(E) [3-(5-{4-[5-(3-Ethoxycarbonylmethyl-phenoxy)-pent-3-en-1-ynyl]-phenyl}-pent-2-en-4-ynyloxy)-phenyl]-acetic acid ethyl ester

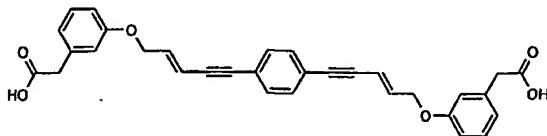


Step C:

- 10 Under an atmosphere of nitrogen, azodicarboxylic dipiperidide (325 mg, 1.3 mmol) was added to a stirred solution of (3-hydroxyphenyl)-acetic acid ethyl ester (340 mg, 1.89 mmol), (E)(E) 5-[4-(5-hydroxy-pent-3-en-1-ynyl)-phenyl]-pent-2-en-4-yn-1-ol (example 1, step A-B)(150 mg, 0.63 mmol) and tributylphosphine (365 mg, 1.3 mmol) in dry THF (30 mL). After 1 h the reaction mixture was added water and the product extracted with ethyl acetate
- 15 (3x). The combined organic phases were washed with water, dried (MgSO_4), filtered and concentrated in vacuo. The crude product was purified by flash chromatography using heptane/ ethyl acetate (4:1) as eluent to give 200 mg of the title compound.
- ^1H NMR (CDCl_3): δ 1.23 (6H, t), 3.55 (4H, s), 4.15 (4H, q), 4.62 (4H, dd), 6.05 (2H, dt), 6.38 (2H, dt), 6.78-6.92 (6H, m), 7.20-7.25 (2H, m), 7.37 (4H, s).

- 20 **Example 22** (General procedure E)

(E)(E) [3-(5-{4-[5-(3-Ethoxycarbonylmethyl-phenoxy)-pent-3-en-1-ynyl]-phenyl}-pent-2-en-4-ynyloxy)-phenyl]-acetic acid



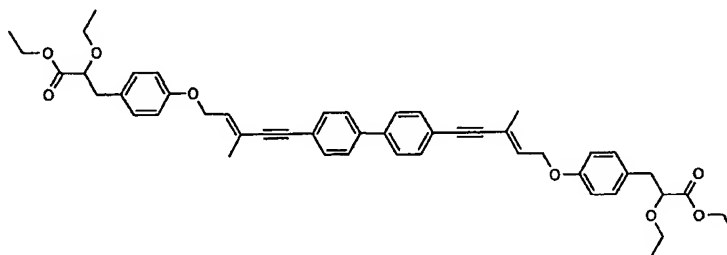
- 25 Step A:

To a solution of (E)(E) [3-(5-{4-[5-(3-ethoxycarbonylmethyl-phenoxy)-pent-3-en-1-ynyl]-phenyl}-pent-2-en-4-ynyloxy)-phenyl]-acetic acid ethyl ester (example 21) (200 mg,

0.35 mmol) in THF (2 mL) and ethanol (6 mL) was added 1N sodium hydroxide (1 mL). After stirring at room temperature for 3 h, the reaction mixture was added 1N hydrochloride acid and ethyl acetate. The title compound was isolated by filtration of the mixture in 50 mg yield. ¹H NMR (DMSO-d₆): δ 3.53 (4H, s), 4.69 (4H, d), 6.16 (2H, d), 6.44 (2H, dt), 6.80-6.92 (6H, m), 7.23 (2H, t), 7.45 (4H, s).

Example 23 (General procedure A)

(E)(E)(S)(S) 2-Ethoxy-3-{4-[5-(4'-[5-[4-(2-ethoxy-2-ethoxycarbonyl)ethyl]-phenoxy]-3-methyl-pent-3-en-1-ynyl)-biphenyl-4-yl]-3-methyl-pent-2-en-4-ynyloxy]-phenyl}-propionic acid ethyl ester



Step A-B:

To a solution of 4,4'-diiodobiphenyl (1.22 g, 3.0 mmol) in diisopropylamine (12 mL) under a nitrogen atmosphere were added copper(I) iodide (30 mg, 0.15 mmol) and tetrakis(triphenylphosphine)palladium (30 mg, 0.03 mmol). After stirring for 1h, a solution of trans-3-methyl-2-pentene-4-yn-1-ol (1.15 g, 12.0 mmol) in diisopropylamine (6 mL) was added. After stirring at 60°C for 8 h, the reaction mixture was filtered and the filtrate evaporated to dryness. The product was purified by flash chromatography using dichloromethane/THF (20:1) as eluent to give 603 mg (59%) of (E)(E) 5-[4'-(5-hydroxy-3-methyl-pent-3-en-1-ynyl)-biphenyl-4-yl]-3-methyl-pent-2-en-4-yn-1-ol.

¹H NMR (DMSO-d₆): δ 1.87 (6H, s), 4.10 (4H, t), 4.80 (2H, t), 6.01 (2H, t), 7.53 (4H, d), 7.73 (4H, d).

Step C:

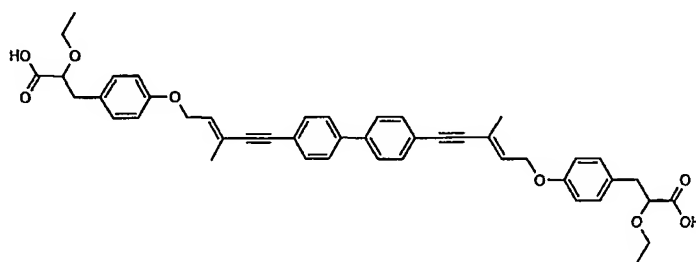
Under a atmosphere of nitrogen, diethyl azodicarboxylate (261 mg, 1.5 mmol) was added at 0-5°C to a stirred solution of (S)-2-ethoxy-3-(4-hydroxyphenyl)-propionic acid ethyl ester (*Tetrahedron Letters*, Vol. 35, No 19, 3139-3142, 1994)(476 mg, 2.0 mmol), (E)(E) 5-[4'-(5-hydroxy-3-methyl-pent-3-en-1-ynyl)-biphenyl-4-yl]-3-methyl-pent-2-en-4-yn-1-ol (171 mg, 0.50 mmol) and triphenylphosphine (393 mg, 1.5 mmol), in dry THF (10 mL). After stirring at 0-5°C for 1h, the reaction mixture was added water and the product extracted with di-

chloromethane (2x). The combined organic phases were dried (MgSO_4), filtered and concentrated in vacuo. The crude product was purified by flash chromatography using dichloromethane/THF (40:1) as eluent to give 213 mg (56%) of the title compound.

^1H NMR (CDCl_3): δ 1.17 (6H, t), 1.22 (6H, t), 2.00 (6H, s), 2.97 (4H, d), 3.30-3.41 (2H, m), 3.55-3.67 (2H, m), 3.97 (2H, t), 4.15 (4H, q), 4.63 (4H, d), 6.18 (2H, dt), 6.85 (4H, d), 7.17 (4H, d), 7.49 (4H, d), 7.57 (4H, d).

Example 24 (General procedure E)

(*E*)(*E*)(*S*)(*S*) 2-Ethoxy-3-{4-[5-(4'-{5-[4-(2-ethoxy-2-ethoxycarbonyl)ethyl]-phenoxy]-3-methyl-pent-3-en-1-ynyl]-biphenyl-4-yl]-3-methyl-pent-2-en-4-ynyloxy]-phenyl}-propionic acid



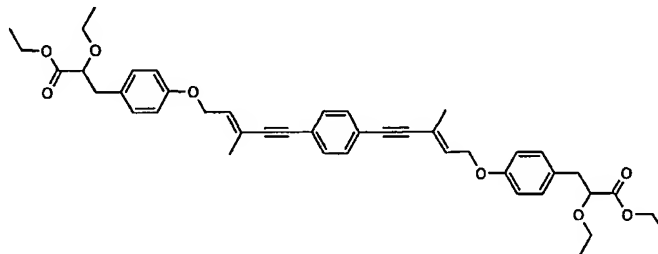
Step A:

To a solution of (*E*)(*E*)(*S*)(*S*) 2-ethoxy-3-{4-[5-(4'-{5-[4-(2-ethoxy-2-ethoxycarbonyl)ethyl]-phenoxy]-3-methyl-pent-3-en-1-ynyl]-biphenyl-4-yl]-3-methyl-pent-2-en-4-ynyloxy]-phenyl}-propionic acid ethyl ester (example 23) (210 mg 0.27 mmol) in ethanol (10 mL) was added 1N sodium hydroxide (2.7 mL). After stirring at 60°C for 30 min, the reaction mixture was concentrated in vacuo and added 1N hydrochloride acid. The product was extracted with dichloromethane (x3). The combined organic phases were dried (MgSO_4), filtered and concentrated in vacuo to give 170 mg (87%) of the title compound.

^1H NMR (CDCl_3): δ 1.19 (6H, t), 2.00 (6H, s), 2.97 (2H, dd), 3.08 (2H, dd), 3.39-3.50 (2H, m), 3.55- 3.68 (2H, m), 4.05 (2H, dd), 4.63 (4H, d), 6.20 (2H, dt), 6.85 (4H, d), 7.18 (4H, d), 7.48 (4H, d), 7.53 (4H, d).

Example 25 (General procedure A)

(E)(E)(S)(S) 2-Ethoxy-3-{4-[5-(4-[5-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-3-methyl-pent-3-en-1-ynyl]-phenyl)-3-methyl-pent-2-en-4-ynyloxy]-phenyl}-propionic acid ethyl ester

5 Step A-B:

To a solution of 1,4-diiodobenzene (0.99 g, 3.0 mmol) in diisopropylamine (12 mL) under a nitrogen atmosphere were added copper(I) iodide (30 mg, 0.15 mmol) and tetrakis(triphenylphosphine)palladium (30 mg, 0.03 mmol). After stirring for 1h, a solution of trans-3-methyl-2-pentene-4-yn-1-ol (1.15 g, 12.0 mmol) in diisopropylamine (6 mL) was added. After stirring at 60°C for 8 h, the reaction mixture was filtered and the filtrate evaporated to dryness. The product was purified by flash chromatography using dichloromethane/THF (20:1) as eluent to give 500 mg (63%) of (E)(E) 5-[4-(5-hydroxy-3-methyl-pent-3-en-1-ynyl)-phenyl]-3-methyl-pent-2-en-4-yn-1-ol.

¹H NMR (DMSO-d₆): δ 1.83 (6H, s), 4.08 (4H, t), 4.80 (2H, t), 5.98 (2H, t), 7.42 (4H, s).

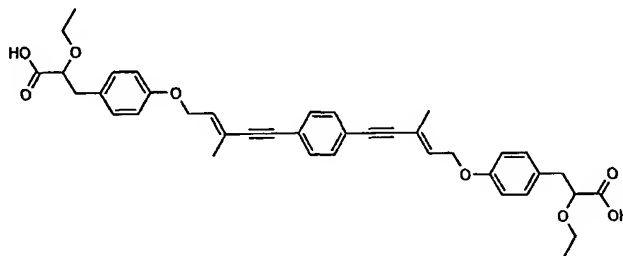
15 Step C:

Under a atmosphere of nitrogen, diethyl azodicarboxylate (261 mg, 1.5 mmol) was added at 0-5°C to a stirred solution of (S)-2-ethoxy-3-(4-hydroxyphenyl)-propionic acid ethyl ester (*Tetrahedron Letters*, Vol. **35**, No 19, 3139-3142, 1994)(476 mg, 2.0 mmol), (E)(E) 5-[4-(5-hydroxy-3-methyl-pent-3-en-1-ynyl)-phenyl]-3-methyl-pent-2-en-4-yn-1-ol (133 mg, 0.50 mmol) and triphenylphosphine (393 mg, 1.5 mmol), in dry THF (10 mL). After stirring at 0-5°C for 1h, the reaction mixture was added water and the product extracted with dichloromethane (2x). The combined organic phases were dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by flash chromatography using dichloromethane/THF (40:1) as eluent to give 290 mg (82%) of the title compound.

25 ¹H NMR (CDCl₃): δ 1.18 (6H, t), 1.23 (6H, t), 1.97 (6H, s), 2.95 (4H, d), 3.30-3.41 (2H, m), 3.53-3.63 (2H, m), 3.98 (2H, t), 4.17 (4H, q), 4.63 (4H, d), 6.18 (2H, dt), 6.82 (4H, d), 7.15 (4H, d), 7.36 (4H, s).

Example 26 (General procedure E)

(E)(E)(S)(S) 2-Ethoxy-3-{4-[5-(4-{5-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-3-methyl-pent-3-en-1-ynyl}-phenyl)-3-methyl-pent-2-en-4-ynyloxy]-phenyl}-propionic acid

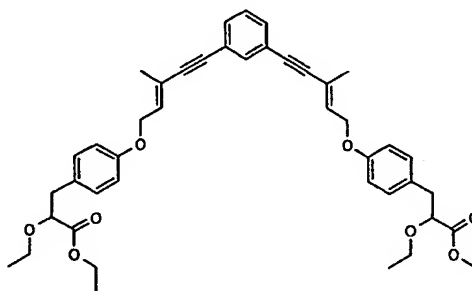
5 **Step A:**

To a solution of (E)(E)(S)(S) 2-ethoxy-3-{4-[5-(4-{5-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-3-methyl-pent-3-en-1-ynyl}-phenyl)-3-methyl-pent-2-en-4-ynyloxy]-phenyl}-propionic acid ethyl ester (example 25) (280 mg 0.40 mmol) in ethanol (10 mL) was added 1N sodium hydroxide (4.0 mL). After stirring at 60°C for 30 min, the reaction mixture
10 was concentrated in vacuo and added 1N hydrochloric acid. The product was extracted with dichloromethane (x3). The combined organic phases were dried (MgSO₄), filtered and concentrated in vacuo to give 241 mg (93%) of the title compound.

¹H NMR (CDCl₃): δ 1.18 (6H, t), 1.98 (6H, s), 2.95 (2H, dd), 3.07 (2H, dd), 3.37-3.49 (2H, m), 3.57- 3.68 (2H, m), 4.04 (2H, dd), 4.62 (4H, d), 6.16 (2H, dt), 6.83 (4H, d), 7.18 (4H, d), 7.36
15 (4H, s).

Example 27 (General procedure A)

(E)(E)(S)(S) 2-Ethoxy-3-{4-[5-(3-{5-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-3-methyl-pent-3-en-1-ynyl}-phenyl)-3-methyl-pent-2-en-4-ynyloxy]-phenyl}-propionic acid ethyl ester



20

Step A-B:

- To a solution of 1,3-diiodobenzene (0.99 g, 3.0 mmol) in diisopropylamine (12 mL) under a nitrogen atmosphere were added copper(I) iodide (30 mg, 0.15 mmol) and tetrakis(triphenylphosphine)palladium (30 mg, 0.03 mmol). After stirring for 1h, a solution of
- 5 trans-3-methyl-2-pentene-4-yn-1-ol (1.15 g, 12.0 mmol) in diisopropylamine (6 mL) was added. After stirring at 60°C for 8 h, the reaction mixture was filtered and the filtrate evaporated to dryness. The product was purified by flash chromatography using dichloromethane/THF (20:1) as eluent to give 780 mg (99%) of (E)(E) 5-[3-(5-hydroxy-3-methyl-pent-3-en-1-ynyl)-phenyl]-3-methyl-pent-2-en-4-yn-1-ol.
- 10 ¹H NMR (DMSO-d₆): δ 1.84 (6H, s), 4.07 (4H, t), 4.82 (2H, t), 6.01 (2H, t), 7.35-7.45 (3H, m), 7.48 (1H, s).

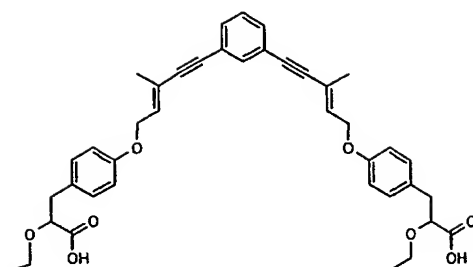
Step C:

- Under a atmosphere of nitrogen, diethyl azodicarboxylate (261 mg, 1.5 mmol) was added at 0°C to a stirred solution of (S)-2-ethoxy-3-(4-hydroxyphenyl)-propionic acid ethyl
- 15 ester (*Tetrahedron Letters*, Vol. 35, No 19, 3139-3142, 1994)(476 mg, 2.0 mmol), (E)(E) 5-[3-(5-hydroxy-3-methyl-pent-3-en-1-ynyl)-phenyl]-3-methyl-pent-2-en-4-yn-1-ol (133 mg, 0.50 mmol) and triphenylphosphine (393 mg, 1.5 mmol), in dry THF (10 mL). After stirring at 0°C for 1h, the reaction mixture was added water and the product extracted with dichloromethane (2x). The combined organic phases were dried (MgSO₄), filtered and concentrated in vacuo.
- 20 The crude product was purified by flash chromatography using dichloromethane/THF (40:1) as eluent to give 250 mg (71%) of the title compound.
- ¹H NMR (CDCl₃): δ 1.18 (6H, t), 1.23 (6H, t), 1.97 (6H, s), 2.95 (4H, d), 3.30-3.41 (2H, m), 3.53-3.63 (2H, m), 3.98 (2H, t), 4.17 (4H, q), 4.63 (4H, d), 6.18 (2H, dt), 6.82 (4H, d), 7.17 (4H, d), 7.20-7.28 (1H, dd), 7.35 (2H, d), 7.52 (1H, s).

25 **Example 28** (General procedure E)

(E)(E)(S)(S) 2-Ethoxy-3-{4-[5-(3-[5-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-3-methyl-pent-3-en-1-ynyl]-phenyl)-3-methyl-pent-2-en-4-ynyloxy]-phenyl}-propionic acid

72

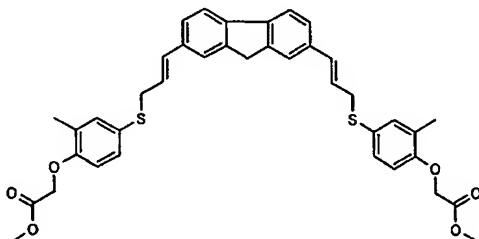
**Step A:**

To a solution of (*E*)(*E*)(*S*)(*S*) 2-ethoxy-3-{4-[5-(3-{5-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-3-methyl-pent-3-en-1-ynyl]-phenyl]-3-methyl-pent-2-en-1-ynyloxy]-phenyl}-propionic acid ethyl ester (example 27) (255 mg 0.36 mmol) in ethanol (10 mL) was added 1N sodium hydroxide (3.6 mL). After stirring at 60°C for 30 min, the reaction mixture was concentrated in vacuo and added 1N hydrochloric acid. The product was extracted with dichloromethane (x3). The combined organic phases were dried (MgSO₄), filtered and concentrated in vacuo to give 232 mg (99%) of the title compound.

¹H NMR (CDCl₃): δ 1.18 (6H, t), 1.98 (6H, s), 2.95 (2H, dd), 3.07 (2H, dd), 3.37-3.49 (2H, m), 3.57- 3.68 (2H, m), 4.04 (2H, dd), 4.62 (4H, d), 6.16 (2H, dt), 6.83 (4H, d), 7.18 (4H, d), 7.25 (1H, dd), 7.35 (2H, d), 7.50 (1H, s).

Example 29

[4-(3-{7-[3-(4-Methoxycarbonylmethoxy-3-methyl-phenylsulfanyl)-propenyl]-9H-fluoren-2-yl}-allylsulfanyl)-2-methyl-phenoxy]-acetic acid methyl ester



(General procedure G)

Step A-B:

A mixture of 2,7-dibromofluorene (Ber. 53, 1236 (1920)) (48.6 g, 0.15 mmol), palladium(II)acetate (1.0 g, 4.45 mmol), triphenylphosphine (3.0 g, 11.4 mmol), triethylamine (30.3 g, 0.3 mol), methyl acrylate (38.7 g, 0.45 mol) and dimethylformamide (150 mL) was stirred

and heated at 110°C for 7 h. The mixture was poured into 1 l water, the resulted solid was filtered off and recrystallized from chloroform to give 36.8 g (74%) of fluorine-2,7-diacrylic acid dimethyl ester. M.p. 206-209 °C.

Step C:

5 A solution of aluminium chloride (19.6 g 0.147 mol) in diethyl ether (150 mL) was added to lithium aluminium hydride (16.6 g, 0.44 mol) in diethyl ether (150 mL) and the mixture was stirred for 30 min. Fluorine-2,7-diacrylic acid dimethyl ester (25.5 g, 76.3 mmol) in THF (1000 mL) was added portionwise to the mixture at 25-50 °C and the stirring was continued for 8 h. 20% NaOH (150 mL) was added dropwise, the suspension was decanted and
10 the organic phase was poured into water (3000 mL). After 3 days in refrigerator 3-[7-(3-hydroxy-propenyl)-9H-fluoren-2-yl-propenol was filtered off and recrystallized from chloroform/methanol yielding 16.5 g (78%) of yellow solid.

¹H NMR (250 MHz, DMSO-d₆): δ 3.88 (2H, s), 4.13 (4H, t), 4.87 (2H, t), 6.40 (2H, dt), 6.60 (2H, d), 7.40 (2H, d), 7.60 (2H, s), 7.77 (2H, d).

15

(General procedure A)

Step C:

a) o-Cresol (100 g, 0.925 mol) was dissolved in 2-butanone (1200 ml), potassium carbonate (191.7 g, 1.5 mol) and ethyl bromoacetate (162.2 g, 0.971 mol) were added and
20 the mixture was refluxed under stirring for 24 h and then left to stand overnight. The solid was filtered off, the filtrate was evaporated and dissolved in benzene (400 ml). The solution was washed with water (200 ml), 5% solution of sodium carbonate (100 ml) and dried over MgSO₄. The residue (cca 200 g) was distilled in vacuo. This afforded 161.9 g (90.1 %) of (2-methyl-phenoxy)-acetic acid ethyl ester, b.p. 120-130 °C/2 kPa.

25 b) Chlorosulfonic acid (180.9 g, 104 ml, 1.553 mol) was cooled to -2 - 0 °C and then the above (2-methyl-phenoxy)-acetic acid ethyl ester (75.35 g, 0.388 mol) was added dropwise under stirring at such rate that the temperature of the reaction mixture did not exceed 0 °C (20 min). The mixture was left to warm to ambient temperature (1 h) and then poured on crushed ice (1 kg). The crystalline product was filtered off, washed with water (500 ml) and
30 dried on air to constant weight. This gave 108.4 g (95.5 %) crude (4-chlorosulfonyl-2-methylphenoxy)-acetic acid ethyl ester. The product was crystallized from cyclohexane (500 ml) affording 73.3 g (64.6 %) pure product. M.p. 86-89 °C.

¹H NMR (300 MHz, CDCl₃): δ 7.84 (2 H, m), 6.80 (1 H, m), 4.76 (2 H, s), 4.29 (2H, q), 2.37 (3 H, s), 1.31 (3 H, s).

c) To the mixture of above (4-chlorosulfonyl-2-methylphenoxy)-acetic acid ethyl ester (97.7 g, 0.333 mol), tin (189.9 g, 1.59 mol) and methanol (170 ml) concentrated hydrochloric acid was added dropwise under vigorous stirring during 20 min. The reaction became exothermic and began to reflux spontaneously. The reaction mixture was further heated to reflux for 3 hours, then cooled and poured to crushed ice (1 kg). The mixture was extracted with diethyl ether (3 x 200 ml), the ethereal solutions were washed with water (2 x 80 ml), dried over MgSO_4 and evaporated in vacuo. The residue (97.7 g) was dissolved in benzene (300 ml), passed through column of silica gel (Fluka 60, 800 g) and the column was washed with benzene (2500 ml). Collected benzene solutions were evaporated and the residue was distilled in vacuo. This afforded 41.3 g (58.4 %) of (4-mercapto-2-methylphenoxy)-acetic acid methyl ester as oil, b.p. 136.5-137 °C/133 Pa.

^1H NMR (250 MHz, CDCl_3): δ 7.04 (m) + 7.04 (m), Σ 2 H, 6.54 (1 H, m), 2.20 (3 H, m), 4.56 (2 H, s), 3.73 (3 H, s), 3.34 (1 H, s).

d) The above 3-[7-(3-hydroxy-propenyl)-9H-fluoren-2-yl]-propenol (85 mg, 0.3 mmol) and tributylphosphine (242 mg, 1.2 mmol) in dry THF (10 mL) was cooled on ice and under an atmosphere of nitrogen added azodicarboxylic dipiperidine (302 mg, 1.2 mmol). After stirring for 10 min at 0 °C, the reaction mixture was slowly added the above (4-mercapto-2-methylphenoxy)-acetic acid methyl ester (255 mg, 1.2 mmol). After stirring at 0 °C for 2 h and at room temperature for 16 h, the reaction mixture was added water (20 mL) and the product extracted with dichloromethane (3x25 mL). The combined organic phases were dried (MgSO_4), filtered and concentrated in vacuo. The crude product was purified by flash chromatography using heptane/ ethyl acetate (5:2) followed by dichloromethane as eluent to give 34 mg (17%) of the title compound.

^1H NMR (CDCl_3): δ 2.25 (6H, s), 3.62 (2H, d), 3.79 (6H, s), 3.85 (2H, s), 4.62 (4H, s), 6.25 (2H, dt), 6.37 (2H, d), 6.62 (2H, d), 7.21 (1H, d), 7.25 (2H, s), 7.28 (2H, d), 7.48 (2H, s), 7.63 (2H, d).

PHARMACOLOGICAL METHODS

In vitro PPARalpha, PPARgamma and PPARdelta activation activity

The PPAR transient transactivation assays are based on transient transfection into human HEK293 cells of two plasmids encoding a chimeric test protein and a reporter protein respectively. The chimeric test protein is a fusion of the DNA binding domain (DBD) from the yeast GAL4 transcription factor to the ligand binding domain (LBD) of the human PPAR proteins. The PPAR-LBD moiety harbored in addition to the ligand binding pocket also the na-

tive activation domain (activating function 2 = AF2) allowing the fusion protein to function as a PPAR ligand dependent transcription factor. The GAL4 DBD will direct the chimeric protein to bind only to Gal4 enhancers (of which none existed in HEK293 cells). The reporter plasmid contained a Gal4 enhancer driving the expression of the firefly luciferase protein. After
5 transfection, HEK293 cells expressed the GAL4-DBD-PPAR-LBD fusion protein. The fusion protein will in turn bind to the Gal4 enhancer controlling the luciferase expression, and do nothing in the absence of ligand. Upon addition to the cells of a PPAR ligand luciferase protein will be produced in amounts corresponding to the activation of the PPAR protein. The amount of luciferase protein is measured by light emission after addition of the appropriate
10 substrate.

CELL CULTURE AND TRANSFECTION

HEK293 cells were grown in DMEM + 10% FCS. Cells were seeded in 96-well plates the day before transfection to give a confluency of 50-80 % at transfection. A total of 0,8 µg DNA containing 0,64 µg pM1α/γLBD, 0,1 µg pCMVβGal, 0,08 µg pGL2(GAL4)₅ and
15 0,02 µg pADVANTAGE was transfected per well using FuGene transfection reagent according to the manufacturers instructions (Roche). Cells were allowed to express protein for 48 h followed by addition of compound.

Plasmids: Human PPAR α, γ and δ was obtained by PCR amplification using cDNA synthesized by reverse transcription of mRNA from human liver, adipose tissue and placenta respectively. Amplified cDNAs were cloned into pCR2.1 and sequenced. The ligand binding domain (LBD) of each PPAR isoform was generated by PCR (PPARα: aa 167 - C-terminus; PPARγ: aa 165 - C-terminus; PPARδ: aa 128 - C-terminus) and fused to the DNA binding domain (DBD) of the yeast transcription factor GAL4 by subcloning fragments in frame into the vector pM1 (Sadowski et al. (1992), Gene 118, 137) generating the plasmids pM1αLBD,
20 pM1γLBD and pM1δ. Ensuing fusions were verified by sequencing. The reporter was constructed by inserting an oligonucleotide encoding five repeats of the GAL4 recognition sequence (5 x CGGAGTACTGTCTCCG(AG)) (Webster et al. (1988), Nucleic Acids Res. 16, 8192) into the vector pGL2 promotor (Promega) generating the plasmid pGL2(GAL4)₅. pCMVβGal was purchased from Clontech and pADVANTAGE was purchased from Promega.

30 IN VITRO TRANSACTIVATION ASSAY

Compounds: All compounds were dissolved in DMSO and diluted 1:1000 upon addition to the cells. Compounds were tested in quadruple in concentrations ranging from 0.001 to 300

μM. Cells were treated with compound for 24 h followed by luciferase assay. Each compound was tested in at least two separate experiments.

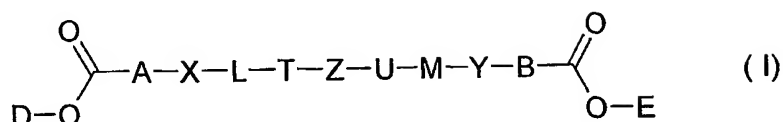
Luciferase assay: Medium including test compound was aspirated and 100 μl PBS incl. 1mM Mg⁺⁺ and Ca⁺⁺ was added to each well. The luciferase assay was performed using the LucLite kit according to the manufacturers instructions (Packard Instruments). Light emission was quantified by counting on a Packard LumiCounter. To measure β-galactosidase activity 25 μl supernatant from each transfection lysate was transferred to a new microplate. β-galactosidase assays were performed in the microwell plates using a kit from Promega and read in a Labsystems Ascent Multiscan reader. The β-galactosidase data were used to normalize (transfection efficiency, cell growth etc.) the luciferase data.

STATISTICAL METHODS

The activity of a compound is calculated as fold induction compared to an untreated sample. For each compound the efficacy (maximal activity) is given as a relative activity compared to Wy14,643 for PPAR α , Rosiglitazone for PPAR γ and Carbacyclin for PPAR δ . The EC₅₀ is the concentration giving 50% of maximal observed activity. EC₅₀ values were calculated via non-linear regression using GraphPad PRISM 3.02 (GraphPad Software, San Diego, Ca). The results were expressed as means \pm SD.

CLAIMS

1. A compound of the general formula (I):



wherein A is C₁₋₃-alkylene which is optionally substituted with one or more substituents selected from

- halogen or
- C₁₋₃-alkyl, C₁₋₆-alkoxy, C₃₋₆-cycloalkoxy, C₁₋₆-alkylthio, C₃₋₆-cycloalkylthio or aralkoxy each of which is optionally substituted with halogen; or
- NR₁R₂ wherein R₁ represents hydrogen or C₁₋₃-alkyl and R₂ represents -R₃-(C=O)-R₄ wherein:
 - R₃ represents C₁₋₆-alkylene, C₂₋₆-alkenylene, C₄₋₆-cycloalkylene, C₄₋₆-cycloalkenylene, or arylene optionally substituted with one or more halogens;
 - R₄ represents aryl optionally substituted with one or more halogens; or

A is -O-A' or -S-A' wherein -O- or -S- is linked to X in formula (I) and wherein A' is C₁₋₃-alkylene which is optionally substituted with one or more substituents selected from

- halogen or
- C₁₋₃-alkyl, C₁₋₆-alkoxy, C₃₋₆-cycloalkoxy, C₁₋₆-alkylthio, C₃₋₆-cycloalkylthio or aralkoxy each of which is optionally substituted with halogen; or
- NR₁R₂ wherein R₁ represents hydrogen or C₁₋₃-alkyl and R₂ represents -R₃-(C=O)-R₄ wherein:
 - R₃ represents C₁₋₆-alkylene, C₂₋₆-alkenylene, C₄₋₆-cycloalkylene, C₄₋₆-cycloalkenylene, or arylene optionally substituted with one or more halogens;
 - R₄ represents aryl optionally substituted with one or more halogens; and

B is C₁₋₃-alkylene which is optionally substituted with one or more substituents selected from

- halogen or

- C₁₋₃-alkyl, C₁₋₆-alkoxy, C₃₋₆-cycloalkoxy, C₁₋₆-alkylthio, C₃₋₆-cycloalkylthio or aralkoxy each of which is optionally substituted with halogen; or
 - NR₁R₂ wherein R₁ represents hydrogen or C₁₋₃-alkyl and R₂ represents -R₃-(C=O)-R₄ wherein:
 - 5 ○ R₃ represents C₁₋₆-alkylene, C₂₋₆-alkenylene, C₄₋₆-cycloalkylene, C₄₋₆-cycloalkenylene, or arylene optionally substituted with one or more halogens;
 - R₄ represents aryl optionally substituted with one or more halogens; or
- 10 B is -O-B' or -S-B' wherein -O- or -S- is linked to Y in formula (I) and wherein B' is C₁₋₃-alkylene which is optionally substituted with one or more substituents selected from
- halogen or
 - C₁₋₃-alkyl, C₁₋₆-alkoxy, C₃₋₆-cycloalkoxy, C₁₋₆-alkylthio, C₃₋₆-cycloalkylthio or aralkoxy each of which is optionally substituted with halogen; or
 - 15 • NR₁R₂ wherein R₁ represents hydrogen or C₁₋₃-alkyl and R₂ represents -R₃-(C=O)-R₄ wherein:
 - R₃ represents C₁₋₆-alkylene, C₂₋₆-alkenylene, C₄₋₆-cycloalkylene, C₄₋₆-cycloalkenylene, or arylene optionally substituted with one or more halogens;
 - 20 ○ R₄ represents aryl optionally substituted with one or more halogens; and
- D is H, C₁₋₆-alkyl or C₃₋₆-cycloalkyl; and
- E is H, C₁₋₆-alkyl or C₃₋₆-cycloalkyl; and
- 25 L and M are independently -O- or -S-; and
- T is C₃₋₉ divalent unsaturated carbon chain optionally substituted with one or more substituents selected from
- 30 • halogen or hydroxy; or
 - aryl, aralkoxy, C₁₋₃-alkoxy which is optionally substituted with halogen; and
- U is C₃₋₉ divalent unsaturated carbon chain optionally substituted with one or more substituents selected from
- 35 • halogen or hydroxy; or

- aryl, aralkoxy, C₁₋₃-alkoxy which is optionally substituted with halogen; and

X is arylene or heteroarylene each of which is optionally substituted with one or more substituents selected from

- 5
- halogen or hydroxy; or
 - C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₁₋₆-alkoxy, C₃₋₆-cycloalkoxy, C₁₋₆-alkylthio, C₃₋₆-cycloalkylthio each of which is optionally substituted with one or more halogen; or

10 Y is arylene or heteroarylene each of which is optionally substituted with one or more substituents selected from

- halogen or hydroxy; or
- C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₁₋₆-alkoxy, C₃₋₆-cycloalkoxy, C₁₋₆-alkylthio, C₃₋₆-cycloalkylthio each of which is optionally substituted with one or more halogen; or

15 Z is arylene, heteroarylene or a divalent polycyclic ringsystem each of which is optionally substituted with one or more substituents selected from

- halogen, oxo or hydroxy; or
- C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₁₋₆-alkoxy, C₃₋₆-cycloalkoxy, C₁₋₆-alkylthio, C₃₋₆-cycloalkylthio each of which is optionally substituted with one or more halogen; or

20

a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, or any tautomeric forms, stereoisomers, mixture of stereoisomers including a racemic mixture, or polymorphs.

25 2. A compound according to claim 1 wherein A is C₁₋₃-alkylene, which is optionally substituted with one or more substituents selected from

- methyl, C₁₋₃-alkoxy, C₃₋₆-cycloalkoxy or benzyloxy each of which is optionally substituted with halogen; or
- NR₁R₂ wherein R₁ represents hydrogen and R₂ represents -R₃-(C=O)-R₄ wherein:

30

 - R₃ represents C₁₋₆-alkylene, C₂₋₆-alkenylene, C₄₋₆-cycloalkylene, C₄₋₆-cycloalkenylene, or phenylene optionally substituted with one or more halogens;
 - R₄ represents phenyl optionally substituted with one or more halogens.

3. A compound according to claim 2 wherein A is methylene or ethylene each of which is optionally substituted with one or more substituents selected from

- methoxy or ethoxy; or
- NR_1R_2 wherein R_1 represents hydrogen and R_2 represents $-\text{R}_3-(\text{C}=\text{O})-\text{R}_4$ wherein R_3 and R_4 represents phenyl.

4. A compound according to any one of the claims 2-3 wherein A is ethylene which is optionally substituted with ethoxy.

5. A compound according to claim 1 wherein A is $-\text{O}-\text{A}'$ or $-\text{S}-\text{A}'$ wherein $-\text{O}-$ or $-\text{S}-$ is linked to X in formula (I) and wherein A' is C_{1-3} -alkylene which is optionally substituted with one or more substituents selected from

- halogen or
- C_{1-3} -alkyl, C_{1-6} -alkoxy, C_{3-6} -cycloalkoxy or aralkoxy each of which is optionally substituted with halogen.

6. A compound according to claim 5 wherein A is $-\text{O}-\text{A}'$ or $-\text{S}-\text{A}'$ wherein $-\text{O}-$ or $-\text{S}-$ is linked to X in formula (I) and wherein A' is methylene or ethylene each of which is optionally substituted with one or more substituents selected from methyl, methoxy or ethoxy.

7. A compound according to any one of the preceding claims wherein B is C_{1-3} -alkylene, which is optionally substituted with one or more substituents selected from

- methyl, C_{1-3} -alkoxy, C_{3-6} -cycloalkoxy or benzyloxy each of which is optionally substituted with halogen; or
- NR_1R_2 wherein R_1 represents hydrogen and R_2 represents $-\text{R}_3-(\text{C}=\text{O})-\text{R}_4$ wherein:
 - R_3 represents C_{1-6} -alkylene, C_{2-6} -alkenylene, C_{4-6} -cycloalkylene, C_{4-6} -cycloalkenylene, or phenylene optionally substituted with one or more halogens;
 - R_4 represents phenyl optionally substituted with one or more halogens.

8. A compound according to claim 7 wherein B is methylene or ethylene each of which is optionally substituted with one or more substituents selected from

- methoxy or ethoxy; or
- NR_1R_2 wherein R_1 represents hydrogen and R_2 represents $-\text{R}_3-(\text{C}=\text{O})-\text{R}_4$ wherein R_3 and R_4 represents phenyl.

9. A compound according to any one of the claims 7-8 wherein B is ethylene which is optionally substituted with ethoxy.

10. A compound according to any one of the claims 1 to 7 wherein B is -O-B' or -S-B' wherein -O- or -S- is linked to Y in formula (I) and wherein B' is C₁₋₃-alkylene which is optionally substituted with one or more substituents selected from

- halogen or
- C₁₋₃-alkyl, C₁₋₆-alkoxy, C₃₋₆-cycloalkoxy or aralkoxy each of which is optionally substituted with halogen.

10

11. A compound according to claim 10 wherein B is -O-B' or -S-B' wherein -O- or -S- is linked to Y in formula (I) and wherein B' is methylene or ethylene each of which is optionally substituted with one or more substituents selected from methyl, methoxy or ethoxy.

12. A compound according to any one of the preceding claims wherein D is H.

13. A compound according to any one of the claims 1 to 11 wherein D is methyl or ethyl.

14. A compound according to any one of the preceding claims wherein E is H.

20

15. A compound according to any one of the claims 1 to 13 wherein E is methyl or ethyl.

16. A compound according to any one of the preceding claims wherein L is -O-.

17. A compound according to any one of the preceding claims wherein L is -S-.

18. A compound according to any one of the preceding claims wherein M is -O-.

19. A compound according to any one of the preceding claims wherein M is -S-.

30

20. A compound according to any one of the preceding claims wherein T is C₃₋₉ divalent unsaturated carbon chain optionally substituted with one or more substituents selected from phenyl, benzyloxy or C₁₋₃-alkoxy which is optionally substituted with halogen.

21. A compound according to claim 20 wherein T is an unsubstituted C₃₋₉ divalent unsaturated carbon chain.
22. A compound according to any one of the claims 20-21 wherein T is C₃₋₉ alkenylene.
23. A compound according to any one of the claims 20-21 wherein T is C₃₋₉ alkynylene.
24. A compound according to any one of the claims 20-21 wherein T is C₅₋₉ alkenynylene.
25. A compound according to any one of the preceding claims wherein U is C₃₋₉ divalent unsaturated carbon chain optionally substituted with one or more substituents selected from phenyl, benzyloxy or C₁₋₃-alkoxy which is optionally substituted with halogen.
26. A compound according to claim 25 wherein U is an unsubstituted C₃₋₉ divalent unsaturated carbon chain.
27. A compound according to any one of the claims 25-26 wherein U is C₃₋₉ alkenylene.
28. A compound according to any one of the claims 25-26 wherein U is C₃₋₉ alkynylene.
29. A compound according to any one of the claims 25-26 wherein U is C₅₋₉ alkenynylene.
30. A compound according to any one of the preceding claims wherein X is arylene or heteroarylene each of which is optionally substituted with one or more substituents selected from
- halogen or
 - C₁₋₆-alkyl optionally substituted with one or more halogen.
31. A compound according to claim 30 wherein X is arylene optionally substituted with one or more substituents selected from
- halogen or
 - C₁₋₆-alkyl optionally substituted with one or more halogen.
32. A compound according to any one of the claims 30-31 wherein X is phenylene optionally substituted with one or more substituents selected from

- halogen or
- C₁₋₃-alkyl optionally substituted with one or more halogen.

33. A compound according to any one of the claims 30 to 32 wherein X is phenylene optionally substituted with one or more halogen.

34. A compound according to any one of the preceding claims wherein Y is arylene or heteroarylene each of which is optionally substituted with one or more substituents selected from

- halogen or
- C₁₋₆-alkyl optionally substituted with one or more halogen.

35. A compound according to claim 34 wherein Y is arylene optionally substituted with one or more substituents selected from

- halogen or
- C₁₋₆-alkyl optionally substituted with one or more halogen.

36. A compound according to any one of the claims 34-35 wherein Y is phenylene optionally substituted with one or more substituents selected from

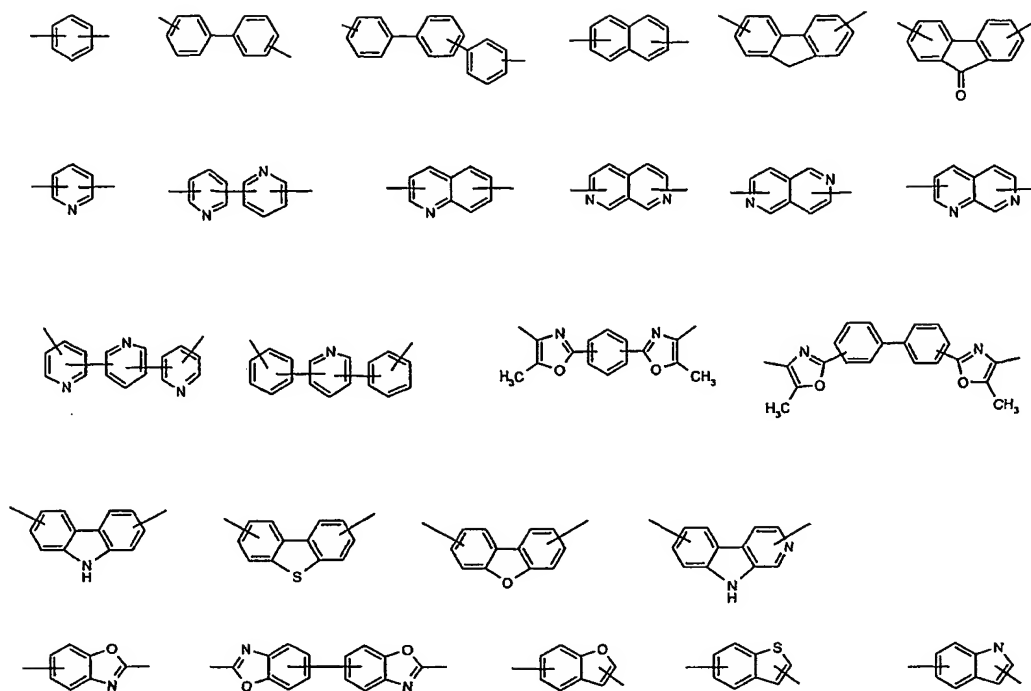
- halogen or
- C₁₋₃-alkyl optionally substituted with one or more halogen.

37. A compound according to any one of the claims 34 to 36 wherein Y is phenylene optionally substituted with one or more halogen.

38. A compound according to any one of the preceding claims wherein Z is arylene, heteroarylene or a divalent polycyclic ringsystem each of which is optionally substituted with one or more substituents selected from

- halogen, oxo or
- C₁₋₆-alkyl, C₁₋₆-alkoxy each of which is optionally substituted with one or more halogen.

39. A compound according to claims 38 wherein Z is selected among the following groups:

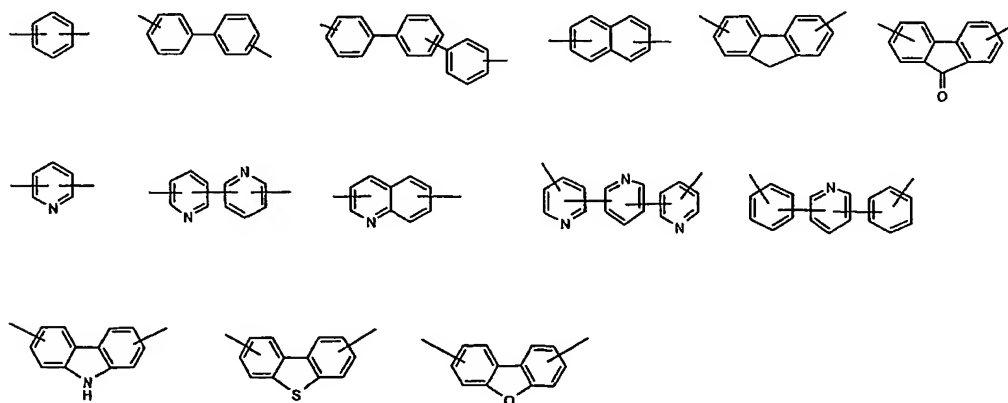


which is optionally substituted with one or more substituents selected from

- halogen or
- C₁₋₆-alkyl or C₁₋₆-alkoxy each of which is optionally substituted with one or more halogen.

40. A compound according to any one of the claims 38-39 wherein Z is selected among the following groups:

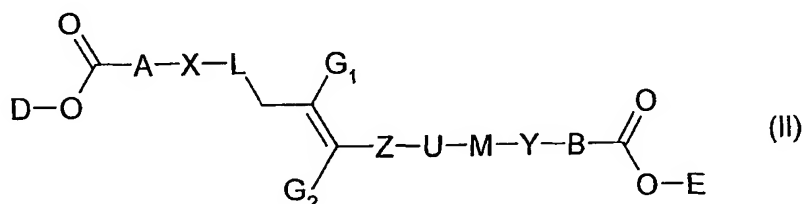
10



41. A compound according to any one of the claims 38 to 40 wherein Z is selected among the following groups:



42. A compound according to claim 1 wherein the general formula (I) as described by the general formula (II):



wherein D, A, X, L, Z, U, M, Y, B and E are as defined in any of the claims 1 to 19 or 25 to 41;

and

G_1 is H, C_{1-3} -alkyl, C_{1-3} -alkoxy or C_{1-3} -aralkoxy each of which is optionally substituted with halogen; and

G_2 is H, C_{1-3} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-6} -alkenynyl, aryl, aralkyl, C_{1-3} -alkoxy or C_{1-3} -aralkoxy each of which is optionally substituted with halogen; or

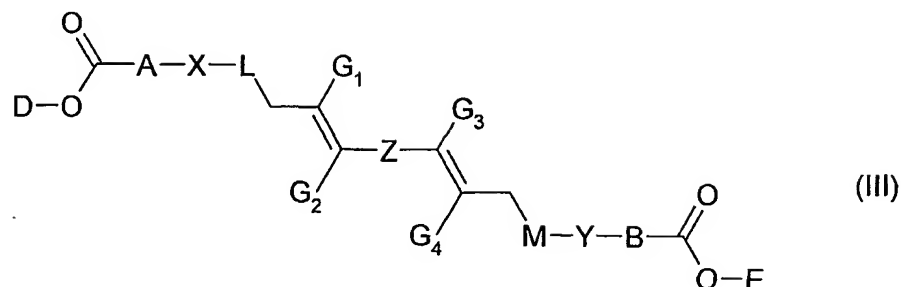
a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, or any tautomeric forms, stereoisomers, mixture of stereoisomers including a racemic mixture, or polymorphs.

43. A compound according to claim 42 wherein G_1 is H, C_{1-3} -alkyl or C_{1-3} -alkoxy each of which is optionally substituted with halogen; and

G_2 is H, C_{1-3} -alkyl or aryl each of which is optionally substituted with halogen.

44. A compound according to any of the claims 42-43 wherein G_1 is H and G_2 is H or methyl.

45. A compound according to claim 1 wherein the general formula (I) as described by the general formula (III):



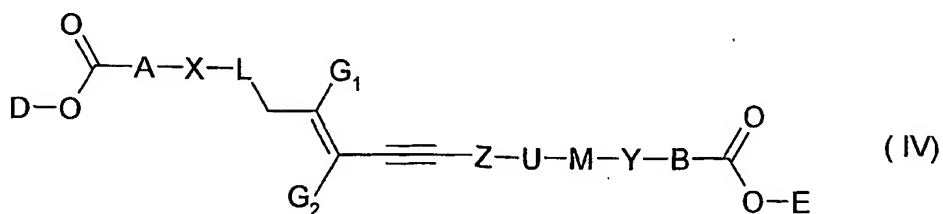
wherein D, A, X, L, Z, M, Y, B and E are as defined in any of the claims 1 to 19 or 30 to 41; and G_1 and G_4 independently of each other are H, C_{1-3} -alkyl, C_{1-3} -alkoxy or C_{1-3} -aralkoxy each of which is optionally substituted with halogen; and

- 5 G_2 and G_3 independently of each other is H, C_{1-3} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-6} -alkenynyl, aryl, aralkyl, C_{1-3} -alkoxy or C_{1-3} -aralkoxy each of which is optionally substituted with halogen; or
a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof,
or any tautomeric forms, stereoisomers, mixture of stereoisomers including a racemic mixture,
10 or polymorphs.

46. A compound according to claim 45 wherein G_1 and G_4 independently of each other are H, C_{1-3} -alkyl or C_{1-3} -alkoxy each of which is optionally substituted with halogen; and
 G_2 and G_3 independently of each other are is H, C_{1-3} -alkyl or aryl each of which is optionally
15 substituted with halogen.

47. A compound according to any of the claims 45-46 wherein G_1 and G_4 are H; and
 G_2 and G_3 independently of each other are H or methyl.

- 20 48. A compound according to claim 1 wherein the general formula (I) as described by the general formula (IV):



wherein D, A, X, L, Z, U, M, Y, B and E are as defined in any of the claims 1 to 19 or 25 to 41;
and

G₁ is H, C₁₋₃-alkyl, C₁₋₃-alkoxy or C₁₋₃-aralkoxy each of which is optionally substituted with halogen; and

- 5 G₂ is H, C₁₋₃-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₆-alkenynyl, aryl, aralkyl, C₁₋₃-alkoxy or C₁₋₃-aralkoxy each of which is optionally substituted with halogen; or
a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof,
or any tautomeric forms, stereoisomers, mixture of stereoisomers including a racemic mixture, or polymorphs.

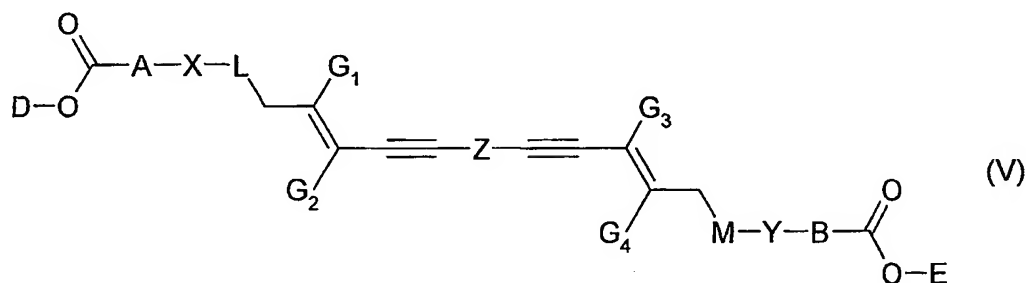
10

49. A compound according to claim 48 wherein G₁ is H, C₁₋₃-alkyl or C₁₋₃-alkoxy each of which is optionally substituted with halogen; and

G₂ is H, C₁₋₃-alkyl or aryl each of which is optionally substituted with halogen.

- 15 50. A compound according to any of the claims 48-49 wherein G₁ is H and G₂ is H or methyl.

51. A compound according to claim 1 wherein the general formula (I) as described by the general formula formula (V):



20

wherein D, A, X, L, Z, M, Y, B and E are as defined in any of the claims 1 to 19 or 30 to 41; and
G₁ and G₄ independently of each other are H, C₁₋₃-alkyl, C₁₋₃-alkoxy or C₁₋₃-aralkoxy each of which is optionally substituted with halogen; and

- 25 G₂ and G₃ independently of each other is H, C₁₋₃-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₆-alkenynyl, aryl, aralkyl, C₁₋₃-alkoxy or C₁₋₃-aralkoxy each of which is optionally substituted with halogen; or

a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, or any tautomeric forms, stereoisomers, mixture of stereoisomers including a racemic mixture, or polymorphs.

- 5 52. A compound according to claim 51 wherein G_1 and G_4 independently of each other are H, C_{1-3} -alkyl or C_{1-3} -alkoxy each of which is optionally substituted with halogen; and G_2 and G_3 independently of each other are H, C_{1-3} -alkyl or aryl each of which is optionally substituted with halogen.
- 10 53. A compound according to any of the claims 51-52 wherein G_1 and G_4 are H; and G_2 and G_3 independently of each other are H or methyl.
54. The compound according to any one of the preceding claims which is:
- 15 2-Ethoxy-3-{4-[5-(4-[5-(4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynyloxy]-phenyl}-propionic acid ethyl ester;
- 3-{4-[5-(4-[5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy]-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynyloxy]-phenyl}-2-ethoxy-propionic acid;
- 3-Chloro-4-(5-{4-[5-(3-Chloro-4-ethoxycarbonylmethyl-phenoxy)-pent-3-en-1-ynyl]-phenyl}-pent-2-en-4-ynyloxy)-phenyl)-acetic acid ethyl ester;
- 20 [4-(5-{4-[5-(4-Carboxymethyl-3-chloro-phenoxy)-pent-3-en-1-ynyl]-phenyl}-pent-2-en-4-ynyloxy)-3-chloro-phenyl]-acetic acid;
- 2-Ethoxy-3-{4-[5-(3-[5-(4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynyloxy]-phenyl}-propionic acid ethyl ester;
- 3-{4-[5-(3-[5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy]-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynyloxy]-phenyl}-2-ethoxy-propionic acid;
- 25 [3-Chloro-4-(5-{3-[5-(2-chloro-4-ethoxycarbonylmethyl-phenoxy)-pent-3-en-1-ynyl]-phenyl}-pent-2-en-4-ynyloxy)-phenyl]-acetic acid ethyl ester;
- [4-(5-{3-[5-(4-Carboxymethyl-2-chloro-phenoxy)-pent-3-en-1-ynyl]-phenyl}-pent-2-en-4-ynyloxy)-3-chloro-phenyl]-acetic acid;
- 30 2-(2-Benzoyl-phenylamino)-3-(4-{5-[4-(5-[4-(2-(2-benzoyl-phenylamino)-2-methoxycarbonyl-ethyl]-phenoxy)-pent-3-en-1-ynyl)-phenyl]-pent-2-en-4-ynyloxy}-phenyl)-propionic acid methyl ester;
- 2-(2-Benzoyl-phenylamino)-3-(4-{5-[4-(5-[4-(2-(2-benzoyl-phenylamino)-2-carboxy-ethyl]-phenoxy)-pent-3-en-1-ynyl)-phenyl]-pent-2-en-4-ynyloxy}-phenyl)-propionic acid;

- 2-Ethoxy-3-{4-[3-(4'-(3-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-1-methyl-propenyl)-biphenyl-4-yl)-but-2-enyloxy]-phenyl}-propionic acid ethyl ester;
 3-{4-[3-(4'-(3-[4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy]-1-methyl-propenyl)-biphenyl-4-yl)-but-2-enyloxy]-phenyl}-2-ethoxy-propionic acid;
 5 2-Ethoxy-3-{4-[5-(7-[5-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-3-methyl-pent-3-en-1-ynyl]-9-oxo-9*H*-fluoren-2-yl)-3-methyl-pent-2-en-4-ynyloxy]-phenyl}-propionic acid ethyl ester;
 3-{4-[5-(7-[5-[4-(2-carboxy-2-ethoxy-ethyl)-phenoxy]-3-methyl-pent-3-en-1-ynyl]-9-oxo-9*H*-fluoren-2-yl)-3-methyl-pent-2-en-4-ynyloxy]-phenyl}-2-ethoxy-propionic acid; or
 10 a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

55. The compound according to any one of any one of the claims 1 to 53 which is:
 [4-(3-{3-[3-(4-Methoxycarbonylmethyl)-phenoxy]-prop-1-ynyl]-phenyl}-prop-2-ynyloxy)-
 15 phenyl]-acetic acid methyl ester;
 [4-(3-{3-[3-(4-Methoxycarbonylmethyl)-phenoxy]-prop-1-ynyl]-phenyl}-prop-2-ynyloxy)-phenyl]-acetic acid;
 [4-(5-{4-[5-(4-Methoxycarbonylmethoxy-3-methyl)-phenoxy]-pent-3-en-1-ynyl]-phenyl}-pent-2-en-4-ynyloxy)-2-methyl-phenoxy]-acetic acid methyl ester;
 20 [4-(5-{4-[5-(4-Methoxycarbonylmethoxy-3-methyl)-phenoxy]-pent-3-en-1-ynyl]-phenyl}-pent-2-en-4-ynyloxy)-2-methyl-phenoxy]-acetic acid;
 3-{3-Bromo-4-[5-(4-[5-[2-bromo-4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-pent-3-en-1-ynyl]-phenyl)-pent-2-en-4-ynyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester;
 3-{3-Bromo-4-[5-(4-[5-[2-bromo-4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-pent-3-en-1-ynyl]-phenyl)-pent-2-en-4-ynyloxy]-phenyl}-2-ethoxy-propionic acid;
 25 [3-(5-{4-[5-(3-Ethoxycarbonylmethyl)-phenoxy]-pent-3-en-1-ynyl]-phenyl}-pent-2-en-4-ynyloxy)-phenyl]-acetic acid ethyl ester;
 [3-(5-{4-[5-(3-Ethoxycarbonylmethyl)-phenoxy]-pent-3-en-1-ynyl]-phenyl}-pent-2-en-4-ynyloxy)-phenyl]-acetic acid;
 30 2-Ethoxy-3-{4-[5-(4'-(5-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-3-methyl-pent-3-en-1-ynyl)-biphenyl-4-yl)-3-methyl-pent-2-en-4-ynyloxy]-phenyl}-propionic acid ethyl ester;
 2-Ethoxy-3-{4-[5-(4'-(5-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-3-methyl-pent-3-en-1-ynyl)-biphenyl-4-yl)-3-methyl-pent-2-en-4-ynyloxy]-phenyl}-propionic acid;
 2-Ethoxy-3-{4-[5-(4-[5-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-3-methyl-pent-3-en-1-ynyl]-phenyl)-3-methyl-pent-2-en-4-ynyloxy]-phenyl}-propionic acid ethyl ester;
 35

- 2-Ethoxy-3-{4-[5-(4-{5-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-3-methyl-pent-3-en-1-ynyl}-phenyl)-3-methyl-pent-2-en-4-ynyloxy]-phenyl}-propionic acid;
- 2-Ethoxy-3-{4-[5-(3-{5-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-3-methyl-pent-3-en-1-ynyl}-phenyl)-3-methyl-pent-2-en-4-ynyloxy]-phenyl}-propionic acid ethyl ester;
- 5 2-Ethoxy-3-{4-[5-(3-{5-[4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenoxy]-3-methyl-pent-3-en-1-ynyl}-phenyl)-3-methyl-pent-2-en-4-ynyloxy]-phenyl}-propionic acid;
- [4-(3-{7-[3-(4-Methoxycarbonylmethoxy-3-methyl-phenylsulfanyl)-propenyl]-9H-fluoren-2-yl}-allylsulfanyl)-2-methyl-phenoxy]-acetic acid methyl ester; or
- a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.
- 10

56. The compound according to any one of the claims 1 to 53, which is:
- (4-(3-(4'-(3-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-propenyl)-biphenyl-4-yl)-allylsulfanyl)-2-methyl-phenoxy)-acetic acid;
- 15 3-(4-(3-(4'-(3-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-propenyl)-biphenyl-4-yl)-allylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- 3-(4-(3-(4'-(3-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-propenyl)-biphenyl-4-yl)-allyloxy)-phenyl)-2-ethoxy-propionic acid;
- 3-(4-(3-(4'-(3-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-propenyl)-biphenyl-4-yl)-allyloxy)-phenyl)-2-ethoxy-propionic acid;
- 20 3-(4-(3-(4'-(3-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-propenyl)-biphenyl-4-yl)-allylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- (4-(3-(4'-(3-(4-Carboxymethoxy-2-chloro-phenoxy)-propenyl)-biphenyl-4-yl)-allylsulfanyl)-2-methyl-phenoxy)-acetic acid;
- 25 (4-(3-(4'-(3-(4-Carboxymethoxy-2-chloro-phenoxy)-propenyl)-biphenyl-4-yl)-allyloxy)-3-chloro-phenyl)-acetic acid;
- 3-(4-(3-(4'-(3-(4-Carboxymethoxy-2-chloro-phenoxy)-propenyl)-biphenyl-4-yl)-allyloxy)-phenyl)-2-ethoxy-propionic acid;
- 3-(4-(3-(4'-(3-(4-Carboxymethoxy-2-chloro-phenoxy)-propenyl)-biphenyl-4-yl)-allylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- 30 (4-(3-(7-(3-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-propenyl)-9H-fluoren-2-yl)-allylsulfanyl)-2-methyl-phenoxy)-acetic acid;
- 3-(4-(3-(7-(3-(4-carboxymethoxy-3-methyl-phenylsulfanyl)-propenyl)-9H-fluoren-2-yl)-allylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- 35

- 3-(4-(3-(7-(3-(4-carboxymethoxy-3-methyl-phenylsulfanyl)-propenyl)-9H-fluoren-2-yl)-allyloxy)-phenyl)-2-ethoxy-propionic acid;
 (4-(3-(7-(3-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-propenyl)-9H-fluoren-2-yl)-allyloxy)-3-chloro-phenyl)-acetic acid;
- 5 3-(4-(3-(7-(3-(4-carboxymethoxy-2-chloro-phenoxy)-propenyl)-9H-fluoren-2-yl)-allylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
 3-(4-(3-(7-(3-(4-carboxymethoxy-2-chloro-phenoxy)-propenyl)-9H-fluoren-2-yl)-allyloxy)-phenyl)-2-ethoxy-propionic acid;
 3-(4-(3-(7-(3-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-propenyl)-9H-fluoren-2-yl)-allyloxy)-phenyl)-2-ethoxy-propionic acid;
- 10 3-(4-(3-(7-(3-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-propenyl)-9H-fluoren-2-yl)-allylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
 (4-(3-(7-(3-(4-Carboxymethoxy-2-chloro-phenyxy)-propenyl)-9H-fluoren-2-yl)-allyloxy)-3-chloro-phenyl)-acetic acid;
- 15 3-(4-(3-(4'-(3-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-1-methyl-propenyl)-biphenyl-4-yl)-but-2-enyloxy)-phenyl)-2-ethoxy-propionic acid;
 3-(4-(3-(4'-(3-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-1-methyl-propenyl)-biphenyl-4-yl)-but-2-enylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- 20 (4-(3-(4'-(3-(4-Carboxymethyl-2-chloro-phenoxy)-1-methyl-propenyl)-biphenyl-4-yl)-but-2-enyloxy)-3-chloro-phenyl)-acetic acid;
 (4-(3-(4'-(3-(4-Carboxymethyl-3-methyl-phenylsulfanyl)-1-methyl-propenyl)-biphenyl-4-yl)-but-2-enylsulfanyl)-2-methyl-phenoxy)-acetic acid;
 3-(4-(3-(4'-(3-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-1-methyl-propenyl)-biphenyl-4-yl)-but-2-enylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- 25 3-(4-(3-(4'-(3-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-1-methyl-propenyl)-biphenyl-4-yl)-but-2-enyloxy)-phenyl)-2-ethoxy-propionic acid;
 3-(4-(3-(4'-(3-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-1-methyl-propenyl)-biphenyl-4-yl)-but-2-enyloxy)-phenyl)-2-ethoxy-propionic acid;
- 30 3-(4-(5-(4-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
 3-(4-(5-(4-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;

- 4-(5-(4-(5-(4-Carboxymethyl-2-chloro-phenoxy)-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynyloxy)-3-chloro-phenyl)-acetic acid;
- 4-(5-(4-(5-(4-Carboxymethyl-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynylsulfanyl)-2-methyl-phenoxy)-acetic acid;
- 5 3-(4-(5-(4-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- 3-(4-(5-(4-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
- 10 3-(4-(5-(4'-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-pent-3-en-1-ynyl)-biphenyl-4-yl)-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
- 3-(4-(5-(4'-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-pent-3-en-1-ynyl)-biphenyl-4-yl)-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- 4-(5-(4'-(5-(4-Carboxymethyl-2-chloro-phenoxy)-pent-3-en-1-ynyl)-biphenyl-4-yl)-pent-2-en-4-ynyloxy)-3-chloro-phenyl)-acetic acid;
- 15 4-(5-(4'-(5-(4-Carboxymethyl-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)-biphenyl-4-yl)-pent-2-en-4-ynylsulfanyl)-2-methyl-phenoxy)-acetic acid;
- 3-(4-(5-(4'-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)-biphenyl-4-yl)-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- 20 3-(4-(5-(4'-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)-biphenyl-4-yl)-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
- (4-(5-(4'-(5-(4-Carboxymethyl-2-chloro-phenoxy)-3-methyl-pent-3-en-1-ynyl)-biphenyl-4-yl)-3-methyl-pent-2-en-4-ynyloxy)-3-chloro-phenyl)-acetic acid;
- 25 (4-(5-(4'-(5-(4-Carboxymethyl-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-biphenyl-4-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-2-methyl-phenoxy)-acetic acid;
- 3-(4-(5-(4'-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-3-methyl-pent-3-en-1-ynyl)-biphenyl-4-yl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
- 3-(4-(5-(4'-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-biphenyl-4-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- 30 3-(4-(5-(4'-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-biphenyl-4-yl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
- 3-(4-(5-(4'-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-biphenyl-4-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;

- 3-(4-(5-(4'-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-biphenyl-4-yl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl-2-ethoxy-propionic acid;
- (4-(5-(4''-(5-(4-Carboxymethyl-2-chloro-phenoxy)-3-methyl-pent-3-en-1-ynyl)-[1,1';4'1'']terphenyl-4-yl)-3-methyl-pent-2-en-4-ynyloxy)-3-chloro-phenyl)-acetic acid;
- (4-(5-(4''-(5-(4-Carboxymethyl-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-[1,1';4'1'']terphenyl-4-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-2-methyl-phenoxy)-acetic acid;
- 3-(4-(5-(4''-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-3-methyl-pent-3-en-1-ynyl)-[1,1';4'1'']terphenyl-4-yl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl-2-ethoxy-propionic acid;
- 3-(4-(5-(4''-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-[1,1';4'1'']terphenyl-4-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-phenyl-2-ethoxy-propionic acid;
- 3-(4-(5-(4''-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-[1,1';4'1'']terphenyl-4-yl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl-2-ethoxy-propionic acid;
- 3-(4-(5-(4''-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-[1,1';4'1'']terphenyl-4-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-phenyl-2-ethoxy-propionic acid;
- 3-(4-(5-(4''-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-[1,1';4'1'']terphenyl-4-yl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl-2-ethoxy-propionic acid;
- 3-(4-(5-(4''-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-pent-3-en-1-ynyl)-[1,1';4'1'']terphenyl-4-yl)-pent-2-en-4-ynyloxy)-phenyl-2-ethoxy-propionic acid;
- 3-(4-(5-(4''-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-pent-3-en-1-ynyl)-[1,1';4'1'']terphenyl-4-yl)-pent-2-en-4-ynylsulfanyl)-phenyl-2-ethoxy-propionic acid;
- 4-(5-(4''-(5-(4-Carboxymethyl-2-chloro-phenoxy)-pent-3-en-1-ynyl)-[1,1';4'1'']terphenyl-4-yl)-pent-2-en-4-ynyloxy)-3-chloro-phenyl)-acetic acid;
- 4-(5-(4''-(5-(4-Carboxymethyl-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)-[1,1';4'1'']terphenyl-4-yl)-pent-2-en-4-ynylsulfanyl)-2-methyl-phenoxy)-acetic acid;
- 3-(4-(5-(4''-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)-[1,1';4'1'']terphenyl-4-yl)-pent-2-en-4-ynylsulfanyl)-phenyl-2-ethoxy-propionic acid;
- 3-(4-(5-(4''-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)-[1,1';4'1'']terphenyl-4-yl)-pent-2-en-4-ynyloxy)-phenyl-2-ethoxy-propionic acid;
- (4-(5-(4-(5-(4-Carboxymethyl-2-chloro-phenoxy)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynyloxy)-3-chloro-phenyl)-acetic acid;
- (4-(5-(4-(5-(4-Carboxymethyl-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynylsulfanyl)-2-methyl-phenoxy)-acetic acid;

- 3-(4-(5-(4-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl-2-ethoxy-propionic acid;
- 3-(4-(5-(4-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynylsulfanyl)-phenyl-2-ethoxy-propionic acid;
- 5 3-(4-(5-(4-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl-2-ethoxy-propionic acid;
- 3-(4-(5-(4-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynylsulfanyl)-phenyl-2-ethoxy-propionic acid;
- 3-(4-(5-(4-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl-2-ethoxy-propionic acid;
- 10 3-(4-(5-(4-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl-2-ethoxy-propionic acid;
- 3-(4-(5-(3-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynyloxy)-phenyl-2-ethoxy-propionic acid;
- 3-(4-(5-(3-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynylsulfanyl)-phenyl-2-ethoxy-propionic acid;
- 15 4-(5-(3-(5-(4-Carboxymethyl-2-chloro-phenoxy)-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynyloxy)-3-chloro-phenyl)-acetic acid;
- 4-(5-(3-(5-(4-Carboxymethyl-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynylsulfanyl)-2-methyl-phenoxy)-acetic acid;
- 20 3-(4-(5-(3-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- 3-(4-(5-(3-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)-phenyl)-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
- 25 4-(5-(3-(5-(4-Carboxymethyl-2-chloro-phenoxy)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynyloxy)-3-chloro-phenyl)-acetic acid;
- 4-(5-(3-(5-(4-Carboxymethyl-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynylsulfanyl)-2-methyl-phenoxy)-acetic acid;
- 3-(4-(5-(3-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl-2-ethoxy-propionic acid;
- 30 3-(4-(5-(3-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynylsulfanyl)-phenyl-2-ethoxy-propionic acid;
- 3-(4-(5-(3-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl-2-ethoxy-propionic acid;

- 3-(4-(5-(3-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
 3-(4-(5-(3-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-phenyl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
- 5 3-(4-(5-(7-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-3-methyl-pent-3-en-1-ynyl)-9-oxo-9H-fluoren-2-yl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
 3-(4-(5-(7-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phensulfanyl)-3-methyl-pent-3-en-1-ynyl)-9-oxo-9H-fluoren-2-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- 10 (4-(5-(7-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)-9-oxo-9H-fluoren-2-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-2-methyl-phenoxy)- acetic acid;
- 3-(4-(5-(7-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-3-methyl-pent-3-en-1-ynyl)-9H-fluoren-2-yl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
- 15 3-(4-(5-(7-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phensulfanyl)-3-methyl-pent-3-en-1-ynyl)- 9H-fluoren-2-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
 (4-(5-(7-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)- 9H-fluoren-2-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-2-methyl-phenoxy)- acetic acid;
- 20 3-(4-(5-(7-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-pent-3-en-1-ynyl)-9-oxo-9H-fluoren-2-yl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
 3-(4-(5-(7-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phensulfanyl)-pent-3-en-1-ynyl)-9-oxo-9H-fluoren-2-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
 (4-(5-(7-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)-9-oxo-9H-fluoren-2-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-2-methyl-phenoxy)- acetic acid;
- 25 3-(4-(5-(7-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-pent-3-en-1-ynyl)-9H-fluoren-2-yl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;
 3-(4-(5-(7-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phensulfanyl)-pent-3-en-1-ynyl)- 9H-fluoren-2-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
- 30 (4-(5-(7-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)- 9H-fluoren-2-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-2-methyl-phenoxy)- acetic acid;
- 35 3-(4-(5-(7-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy)-3-methyl-pent-3-en-1-ynyl)-9H-carbazol-2-yl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;

3-(4-(5-(7-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phensulfanyl)-3-methyl-pent-3-en-1-ynyl)- 9H-carbazol-2-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;
 (4-(5-(7-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-3-methyl-pent-3-en-1-ynyl)- 9H-carbazol-2-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-2-methyl-phenoxy)- acetic acid;

5

3-(4-(5-(7-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phenoxy-pent-3-en-1-ynyl)-9H-fluoren-2-yl)-3-methyl-pent-2-en-4-ynyloxy)-phenyl)-2-ethoxy-propionic acid;

3-(4-(5-(7-(5-(4-(2-Carboxy-2-ethoxy-ethyl)-phensulfanyl)-pent-3-en-1-ynyl)- 9H- carbazol-2-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-phenyl)-2-ethoxy-propionic acid;

10 (4-(5-(7-(5-(4-Carboxymethoxy-3-methyl-phenylsulfanyl)-pent-3-en-1-ynyl)- 9H- carbazol-2-yl)-3-methyl-pent-2-en-4-ynylsulfanyl)-2-methyl-phenoxy)- acetic acid; or
 a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

15 57. Use of a compound according to any one of the preceding claims as a pharmaceutical composition.

58. A pharmaceutical composition comprising, as an active ingredient, at least one compound according to any one of the claims 1 to 56 together with one or more
 20 pharmaceutically acceptable carriers or excipients.

59. A pharmaceutical composition according to claim 58 in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably from about 0.1 to about 500 mg of and especially preferred from about 0.5 mg to about 200 mg per day of compound according to
 25 any one of the claims 1 to 56.

60. A pharmaceutical composition for the treatment of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR), the composition comprising a compound according to any one of the claims 1 to 56 together with
 30 one or more pharmaceutically acceptable carriers or excipients.

61. A pharmaceutical composition for the treatment of type I diabetes, type II diabetes, dyslipidemia, syndrome X (including the metabolic syndrome, i.e. impaired glucose tolerance, insulin resistance, hypertriglyceridaemia and/or obesity), cardiovascular diseases
 35 (including atherosclerosis) or hypercholesteremia comprising a compound according to any

of the claims 1 to 56 together with one or more pharmaceutically acceptable carriers or excipients.

62. A pharmaceutical composition according to any one of the claims 58 to 61 for oral, nasal,
5 transdermal, pulmonal, or parenteral administration.

63. Use of a compound according to any one of the claims 1 to 56 for the preparation of a
pharmaceutical composition for the treatment of conditions mediated by nuclear receptors, in
particular the Peroxisome Proliferator-Activated Receptors (PPAR).
10

64. Use of a compound according to any one of claims 1 to 56 for the preparation of a
pharmaceutical composition for the treatment of type I diabetes or type II diabetes.

65. Use of a compound according to any one of claims 1 to 56 for the preparation of a
15 pharmaceutical composition for the treatment of dyslipidemia.

66. Use of a compound according to any one of claims 1 to 56 for the preparation of a
pharmaceutical composition for the treatment of syndrome X including the metabolic
syndrome, i.e. impaired glucose tolerance, insulin resistance, hypertriglyceridaemia and/or
20 obesity.

67. Use of a compound according to any one of claims 1 to 56 for the preparation of a
pharmaceutical composition for the treatment of cardiovascular diseases including
atherosclerosis.
25

68. Use of a compound according to any one of claims 1 to 56 for the preparation of a
pharmaceutical composition for the treatment of hypercholesteremia.

69. A method for the treatment of conditions mediated by nuclear receptors, in particular the
30 Peroxisome Proliferator-Activated Receptors (PPAR), the method comprising administering
to a subject in need thereof an effective amount of a compound according to any one of the
claims 1 to 56 or a pharmaceutical composition comprising the same.

70. A method for the treatment of type I diabetes, type II diabetes, dyslipidemia, syndrome X
35 (including the metabolic syndrome, i.e. impaired glucose tolerance, insulin resistance,

hypertriglyceridaemia and/or obesity), cardiovascular diseases (including atherosclerosis) or hypercholesteremia, the method comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 1 to 56 or of a pharmaceutical composition comprising the same.

5

71. The method according to claims 69 or 70 wherein the effective amount of the compound according to any one of the claims 1 to 56 is in the range of from about 0.05 mg to about 1000 mg, preferably from about 0.1 to about 500 mg of and especially preferred from about 0.5 mg to about 200 mg per day.

10

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 02/00692

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C69/734 C07C59/68 C07C229/36 C07C59/90 A61K 31/225,
A61K31/194 A61P9/00 A61P3/06 A61P3/10 A61P3/04
C07C69/712 C07C323/21

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01 55086 A (NOVO NORDISK AS) 2 August 2001 (2001-08-02) page 1, line 6 - line 11 examples 1-25 ---	1,57,58, 60,61, 63-70
A	WO 01 55085 A (NOVO NORDISK AS) 2 August 2001 (2001-08-02) page 1, line 6 - line 10 examples 151,152 ---	1,57,58, 60,61, 63-70
A	EP 0 597 102 A (YAMANOUCHI PHARMA CO LTD) 18 May 1994 (1994-05-18) page 1, line 3 - line 6 examples 2-4 ---	1,57,58, 60,61, 63-70
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

13 January 2003

Date of mailing of the international search report

20/01/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Kardinal, S

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 02/00692

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT.

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>US 4 148 915 A (THUILLIER GERMAINE ET AL) 10 April 1979 (1979-04-10)</p> <p>the whole document -----</p>	<p>1,57,58, 60,61, 63-70</p>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 02/00692.

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 69-71 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/DK 02/00692

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0155086	A	02-08-2001	AU 2831801 A BR 0107902 A WO 0155086 A1 EP 1254102 A1 NO 20023567 A US 2001041709 A1	07-08-2001 05-11-2002 02-08-2001 06-11-2002 25-09-2002 15-11-2001
WO 0155085	A	02-08-2001	AU 2831901 A BR 0107901 A WO 0155085 A1 EP 1254101 A1 NO 20023566 A	07-08-2001 05-11-2002 02-08-2001 06-11-2002 25-09-2002
EP 0597102	A	18-05-1994	AU 663514 B2 DE 69228122 D1 DE 69228122 T2 DK 597102 T3 EP 0597102 A1 FI 940419 A KR 204938 B1 NO 940312 A US 5508296 A AT 175409 T AU 2346592 A CA 2114001 A1 ES 2128355 T3 HU 70421 A2 WO 9303021 A1	12-10-1995 18-02-1999 24-06-1999 09-08-1999 18-05-1994 28-01-1994 15-06-1999 17-03-1994 16-04-1996 15-01-1999 02-03-1993 18-02-1993 16-05-1999 30-10-1995 18-02-1993
US 4148915	A	10-04-1979	FR 2331336 A1 AR 212749 A1 AU 1951676 A BE 848310 A1 CH 598179 A5 CS 191324 B2 DD 127468 A5 DE 2651500 A1 ES 453309 A1 FR 2381017 A2 GB 1561561 A HU 172710 B JP 52093726 A LU 76183 A1 NL 7612515 A PL 103867 B1 PT 65835 A ,B	10-06-1977 29-09-1978 18-05-1978 12-05-1977 28-04-1978 29-06-1979 28-09-1977 26-05-1977 16-11-1977 15-09-1978 27-02-1980 28-11-1978 06-08-1977 03-06-1977 17-05-1977 31-07-1979 01-12-1976